

Research Article



## Anti-Inflammatory Effect of Taurine in Burned Patients

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### Abstract

**Purpose:** Burn induced inflammatory response can be mediated by reactive oxygen metabolites and accompanied by multiple organ dysfunction. Taurine has protective effects against various inflammatory conditions. The aim of this study was to determine the effect of Taurine supplement in thermal burn victims.

**Methods:** Thirty patients with severe thermal burns were enrolled in this randomized double-blinded clinical trial. These patients were randomly divided into two equal groups (namely Control and Taurine groups), where both received isocaloric and isonitrogenous formula. One group was supplemented with 50 mg/kg of Taurine per day for a duration of 10 days. Blood samples were obtained to measure Interleukin-10 (IL-10), high-sensitivity C-reactive protein (hs-CRP), and Tumor Necrosis Factor alpha (TNF- $\alpha$ ) levels at the beginning and the end of the study.

**Results:** Change in serum level of IL-10 in Taurine group was more than Control group [-13.60(-31.40, -10.40) compared to -4.00(-20.00, -0.20) respectively;  $P = 0.030$ ]. This change was significant in patients with more than 30% TBSA of burn [-14.20(-31.40, -10.40) compared to -2.40(-9.60, 0.40) respectively;  $P = 0.013$ ]. As for the hs-CRP and TNF- $\alpha$  levels, the difference between the two groups were not significant.

**Conclusion:** Based on the results obtained, Taurine supplement showed a positive outcome on anti-inflammatory cytokine IL-10 in all burn patients. This effect was even more significant in patients with higher percentage of burn area. Taurine had no significant effect on the inflammatory marker hs-CRP and the pro-inflammatory cytokine TNF- $\alpha$  level. For a more thorough verification, measurement of a wider range of inflammatory cytokines in more frequent time intervals are suggested.

### Introduction

Extensive tissue destruction are the major causes of mortality and morbidity. Following the initial resuscitation period, patients develop systemic inflammatory response syndrome (SIRS).<sup>1</sup> The activation of a pro-inflammatory cascade after burn injury appears to be important in the development of subsequent immune dysfunction, susceptibility to sepsis, and development of SIRS and multiple organ dysfunction syndrome (MODS), which primarily contribute to morbidity and mortality in severe burn injuries.<sup>2</sup> Following the initial pro-inflammatory phase, anti-inflammatory response follows primarily as a release of IL-10, IL-4, prostaglandin E2, soluble TNF receptors and IL-1 receptor antagonists.<sup>3</sup> The temporal relationship between a pro-inflammatory and anti-inflammatory cytokine response is not fully understood but anti-inflammatory mediators are known to suppress the cellular immune response. The anti-inflammatory response overcome the pro-inflammatory state, leading to

a functional state of depressed immune response. This state causes, impaired antibody production and diminished phagocytosis, which puts patients in an increased risk for additional infectious state.<sup>4,5</sup> IL-10 is an important anti-inflammatory cytokine. It is classified as a Th2-type cytokine and known to be an important factor in maintaining homeostasis of overall immune responses.<sup>6,7</sup> With its immunosuppressive properties, IL-10 is produced by monocytes and T helper cells, including activated T cells and B cells.<sup>8</sup> In addition, it has been shown to suppress a wide range of inflammatory responses. Taurine (2-aminoethylsulphonic acid) is derived from the methionine and cysteine metabolism. As a semi-essential amino acid with high concentration in mammalian cells and plasma, Taurine plays an important role in various essential biological processes.<sup>9,10</sup> Taurine is presented in neutrophilic granulocytes, lymphocytes and monocytes.<sup>11,12</sup> It is an antioxidant and has tissue

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protective effects in oxidant induced injuries. It can reduce cell injuries followed by ischemia and reperfusion phenomena.<sup>13-15</sup> It is effective in the maintenance of vascular tone and exerts a vasodilator,<sup>16</sup> osmoregulator, intracellular calcium canal regulator effects. As part of an anti-inflammatory process, Taurine (within monocytes and neutrophils) reacts with hypochlorous acid (HOCL) to produce Taurine chloramines (TauCL). TauCL is less toxic than HOCL and is a powerful regulator of inflammation. It regulates the pro-inflammatory mediators in inflammatory cells.<sup>17,18</sup>

In this study, we aimed to investigate the levels of pro-inflammatory and anti-inflammatory cytokines over a time interval (days 1 and 9), in order to determine the relationship between the effects of Taurine and the levels of these cytokines (IL-10, hs-CRP, and TNF- $\alpha$ ) on burned patients.

### Materials and Methods

This was an interventional study, single-centre, double-blind, and block Randomised Clinical Trial. It was conducted on 30 patients with severe burns, admitted to the Burns Ward of Sina Hospital (Tabriz, Iran).

#### Eligibility Criteria

**Inclusion Criteria** – Patients in this study were admitted within the first day of obtaining a burn injury, with a Total Body Surface Area (TBSA) of burn with greater than 20%. The age range was between 18-85 years with an expected hospital stay of 10 days. These patients were likely to have at least 48 hours of enteral nutrition.

**Exclusion Criteria** – Pregnant women, patients with cardiogenic shock, severe inhalation injury, hepatic failure, renal failure, congenital amino acid metabolism impairment, and enteral feeding contraindication were excluded from this study.

**Age Limits** – The age limit was above 18 years of age.

#### Experimental Design

The patients were divided into two groups of 15 by a random allocation software. One group was defined as the Control group and consisted of 10 males and 5 females aged between 18 to 60 years of age (Group C: n = 15, Age Range 18-60, Average  $36.27 \pm 14.35$ ). The second group, defined as Taurine group, also consisted of 10 males and 5 females with an age range between 21 to 72 years (Group T: n = 15, Age Range 21-72, Average  $37.38 \pm 14.08$ ). Both groups received the routine therapy for management of burns after admission.

#### Nutrition

All the subjects received hourly enteral feeding of commercially prepared meal (EnteraMeal Standard Karen Pharma and Food supplement Co., Iran),  $1\text{kcal.ml}^{-1}$ : 14% Protein, 54% Carbohydrate, and 32% Fat) within the first hour of admission. Protein was also added to patients with burns more than 30% TBSA starting day 3. This was to maintain their protein levels at about  $1.5\text{-}2\text{ mg.kg}^{-1}$ . The composition of the diet was identical for each group. The

calorie requirement was calculated according to the Harris-Benedict equation which gives an estimate of Resting Energy Expenditure (REE) x 1.5. Taurine group received an additional daily intake of Taurine supplement (Euro OTC Pharma GmbH, Germany) of  $50\text{ mg.kg}^{-1}$  (with a maximum dose of 4g per day). This intervention lasted for about 10 days from the admission day used as the baseline and the second blood sample measurement on day 9.

#### Biochemical Assessment

Blood samples were obtained on days 1 and 9 after injury in order to measure IL-10, hs-CRP and TNF- $\alpha$  levels. Serum were separated immediately after centrifugation and frozen at  $-70^{\circ}\text{C}$  until it was assayed. Serum levels of IL-10, TNF- $\alpha$ , and hs-CRP were measured using commercially available Enzyme-Linked Immunosorbant Assay (ELISA) kits (eBioscience, Austria).

#### Statistical Analysis

Data were analysed using SPSS (Version 21). Data distribution was assessed using Kolmogorov-Smirnov test. Normally distributed variables were presented as Mean  $\pm$  Standard Deviation ( $M \pm SD$ ). Comparison of time points (Day 1 and Day 9) within each group was assessed by Dependent (Paired) Samples t-test. Comparisons between groups were made with Independent (Unpaired) Samples t-test. Non-normally distributed variables were presented as the Median and Interquartile Range (IQR) (standard 25<sup>th</sup>-75<sup>th</sup> percentile). Comparisons of non-normally distributed samples were performed using Wilcoxon Signed-Ranks test within each group, and Mann-Whitney U test to compare differences between the two groups. The probability less than 0.05 ( $P < 0.05$ ) were considered significant.<sup>19</sup>

#### Results

General characteristics of the patients are shown in Table 1. The majority of the patients were male (66.7%). The age range was between 18-72 years (n=30; age average of  $36.27 \pm 14.86$  in Group C and  $37.73 \pm 14.57$  in Group T; Table 1). The Extent of Total Body Surface Area (TBSA) in all the burn patients ranged between 20% and 60% (TBSA%:  $31.07 \pm 12.40$  in Group C and  $32.33 \pm 12.25$  in Group T; Table 1).

**Table 1.** Characteristics of Study Subjects

| Characteristics               | Group C (n=15)     | Group T (n=15)    |
|-------------------------------|--------------------|-------------------|
| Age <sup>1</sup> (yr)         | $36.27 \pm 14.86$  | $37.73 \pm 14.57$ |
| Age Range (yr)                | 18-60              | 21-72             |
| Sex <sup>2</sup> (M:F)        | 10:5               | 10:5              |
| Weight <sup>1</sup> (kg)      | $72.67 \pm 17.99$  | $68.33 \pm 14.68$ |
| Height <sup>1</sup> (cm)      | $167.13 \pm 12.30$ | $167.27 \pm 7.03$ |
| TBSA <sup>1</sup> (%)         | $31.07 \pm 12.40$  | $32.33 \pm 12.25$ |
| TBSA < 30%                    | $22.25 \pm 2.76$   | $23.13 \pm 2.80$  |
| TBSA $\geq$ 30%               | $41.14 \pm 11.29$  | $42.86 \pm 9.94$  |
| Sepsis <sup>3</sup> (n, %)    | 2, 13.33           | 1, 6.67           |
| Mortality <sup>3</sup> (n, %) | 1, 6.67            | 1, 6.67           |

<sup>1</sup> Data for Age, Weight, Height, and TBSA are presented as Means  $\pm$  Standard Deviation ( $M \pm SD$ )

<sup>2</sup> Data for Sex are presented as frequency ratio (Male:Female)

<sup>3</sup> Data for Sepsis and Mortality are presented as Frequency and Percentage (Frequency, Percentage)

Patients in T group had a more significant decreased levels of IL-10 compared with C group subjects (-13.60[-31.40, -10.40] compared with -4.00[-20.00, -0.20] respectively;  $P = 0.030$ ; Table 2). In particular, patients with severe burn (TBSA  $\geq 30\%$ ) showed a more significant change (-14.20[-31.40, -10.40] compared with -2.40[-9.60, 0.40] respectively;  $P = 0.013$ ; Table 2). Hs-CRP levels were increased in group C ( $0.83 \pm 1.54$ ;  $P = 0.056$ , Table 2) while group T showed a non-significant decrease ( $-0.46 \pm 2.33$ ;  $P > 0.05$ , Table 2).

The difference between the two groups was not significant ( $P = 0.087$ ; Table 2). There was no significant difference between the two groups based on severity. Plasma TNF- $\alpha$  levels increased significantly in Control group ( $0.71 \pm 1.42$ ;  $P = 0.038$ , Table 2). There was a non-significant increase in TNF- $\alpha$  levels of group T ( $0.08 \pm 1.57$ ;  $P > 0.05$ , Table 2). The difference between the two groups was not significant ( $P = 0.131$ ; Table 2). Comparing the two groups based on severity of burn did not show any significance neither.

**Table 2.** Effect of Taurine Supplement on Inflammatory Markers

| Variable                                   | Group C                            |                                    |              | Group T                            |                                    |              | P**          |
|--|------------------------------------|------------------------------------|--------------|------------------------------------|------------------------------------|--------------|--------------|
|  | Day 1                              | Day 9                              | P*           | Day 1                              | Day 9                              | P*           |              |
| <b>IL-10<sup>1</sup></b>                   | <b>19.20 (6.40,26.80)</b>          | <b>6.60 (5.40,10.40)</b>           | <b>0.004</b> | <b>25.60 (15.00,44.60)</b>         | <b>7.20 (5.40,13.20)</b>           | <b>0.001</b> | <b>0.030</b> |
| IL-10 <sup>1</sup> < 30%                   | 24.10 (7.15,29.05)                 | 5.80 (5.10, 9.40)                  | 0.013        | 23.70 (15.75,74.78)                | 6.90 (4.65, 8.60)                  | 0.006        | 0.377        |
| IL-10 <sup>1</sup> $\geq 30\%$             | 9.00 (6.40, 26.80)                 | 9.60 (6.60,17.80)                  | 0.102        | 29.40 (13.00,44.60)                | 7.20 (5.60,13.20)                  | 0.009        | 0.013        |
| <b>hs-CRP<sup>2</sup></b>                  | <b>7.99 <math>\pm</math> 1.77</b>  | <b>8.82 <math>\pm</math> 1.09</b>  | <b>0.056</b> | <b>8.89 <math>\pm</math> 1.56</b>  | <b>8.43 <math>\pm</math> 1.52</b>  | <b>0.458</b> | <b>0.087</b> |
| hs-CRP <sup>2</sup> < 30%                  | 6.99 $\pm$ 1.37                    | 8.46 $\pm$ 0.82                    | 0.025        | 8.24 $\pm$ 1.86                    | 7.85 $\pm$ 1.85                    | 0.745        | 0.168        |
| hs-CRP <sup>2</sup> $\geq 30\%$            | 9.15 $\pm$ 1.48                    | 9.24 $\pm$ 1.28                    | 0.434        | 9.63 $\pm$ 3.38                    | 9.09 $\pm$ 3.18                    | 0.060        | 0.156        |
| <b>TNF-<math>\alpha</math><sup>2</sup></b> | <b>10.76 <math>\pm</math> 0.81</b> | <b>11.11 <math>\pm</math> 0.90</b> | <b>0.038</b> | <b>11.11 <math>\pm</math> 1.12</b> | <b>11.19 <math>\pm</math> 1.41</b> | <b>0.423</b> | <b>0.131</b> |
| TNF- $\alpha$ <sup>2</sup> < 30%           | 10.45 $\pm$ 0.65                   | 11.63 $\pm$ 1.17                   | 0.043        | 10.90 $\pm$ 0.95                   | 11.68 $\pm$ 1.03                   | 0.088        | 0.309        |
| TNF- $\alpha$ <sup>2</sup> $\geq 30\%$     | 11.11 $\pm$ 0.88                   | 11.29 $\pm$ 0.49                   | 0.322        | 11.36 $\pm$ 4.20                   | 10.64 $\pm$ 3.72                   | 0.108        | 0.093        |

<sup>1</sup> Data for IL-10 is presented as Median (IQR)

<sup>2</sup> Data for hs-CRP and TNF- $\alpha$  are presented as Means  $\pm$  Standard Deviation (M  $\pm$  SD)

\* Indicates the P value comparing time points within a single group using Paired t-test or Wilcoxon Signed-Rank test

\*\* Indicates the P value comparing the mean difference between two groups using Unpaired t-test or Mann-Whitney test

## Discussion

The aim of this study was to assess the administration of a Taurine supplement and its effect on the inflammatory response in severely burned patients.

The survival rates for burn patients have improved significantly over the last few decades due to advances in intensive care and burn centers. Burn wound infection is caused by impaired systematic and local immune responses. The functional integrity of immune responses after injury is very important. Several studies have reported an elevated levels of macrophage derived mediators in tissues of burned animals and patients, including TNF- $\alpha$ , which in turn influence lymphocyte responses. This dysregulation of macrophage activity leads to increased pro-inflammatory factors and increased susceptibility to sepsis.<sup>20</sup>

Usually, the exceeding release of pro-inflammatory cytokines is only short lived, whereas the suppression of the cellular defence function mediated by anti-inflammatory cytokines and other mediators lasts longer. This suppression may prompt a new episode of infection and subsequently may trigger a new peak of the systemic inflammatory response.<sup>21</sup>

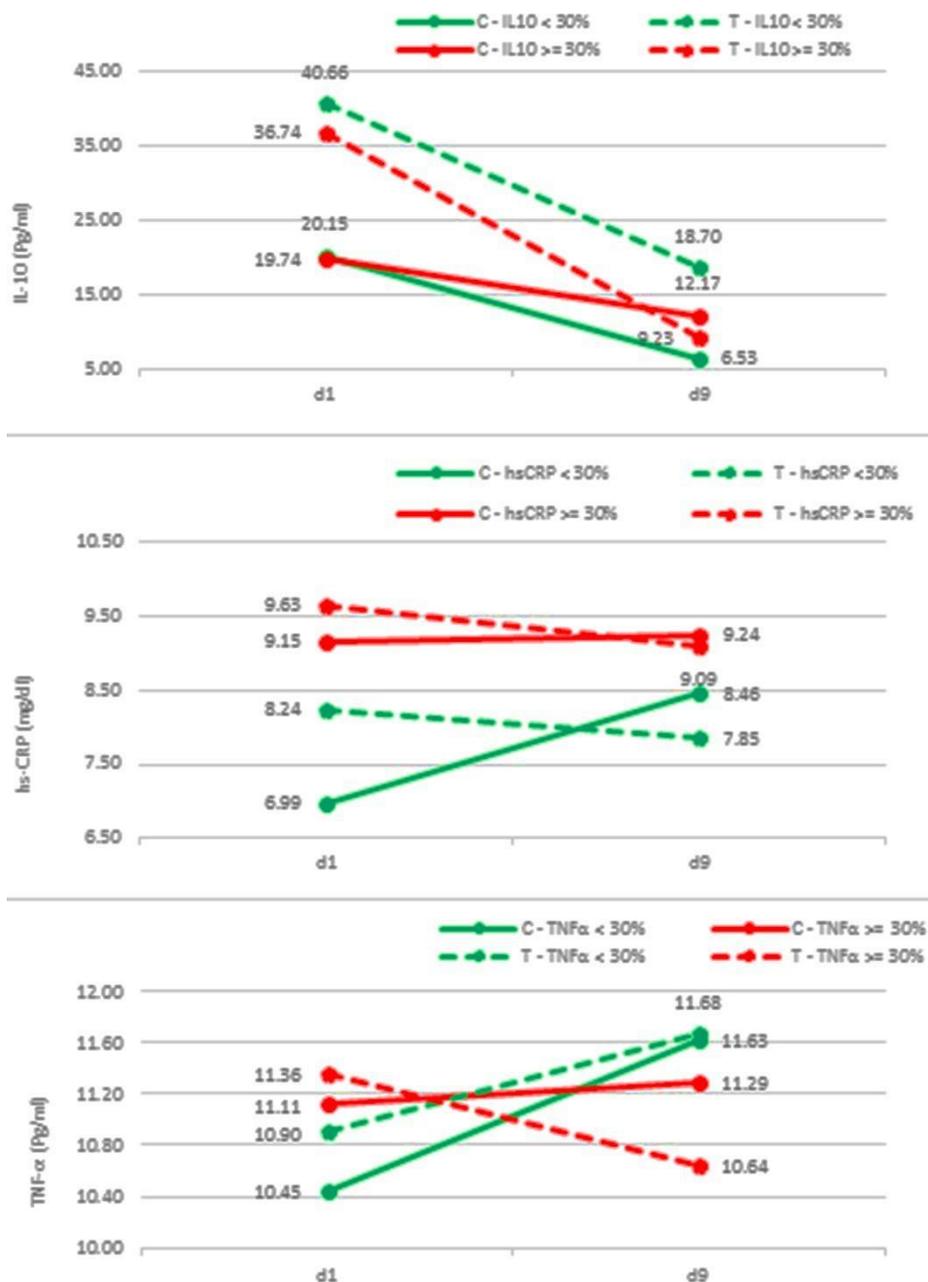
Septic patients are characterized by their inability to eliminate invading pathogens and susceptibility to secondary nosocomial infections. In injured patients, an increased production of IL-10 is correlated with subsequent sepsis.<sup>22</sup> This increase which occurs in burn injuries, results in a deficient immune response to infection and an increase in sepsis-related mortality.<sup>23</sup>

Lyons et al. showed that in a burned mouse, this cytokine decreases resistance to infection.<sup>22</sup>

Taurine can provide a range of benefits through its antioxidant and anti-inflammatory effects. It also has been shown to be tissue- protective in variety of models which result in inflammation.<sup>17</sup> Taurine can act as a trap for HOCl forming the long-lived oxidant Tau-NHCl, which is more stable and less toxic than HOCl. Moreover, Tau-NHCl down-regulates the generation of pro-inflammatory mediators by phagocytic cells, such as TNF- $\alpha$  and IL-1 $\beta$ .<sup>17,18</sup> This process suppresses the inflammatory reaction and protects cells from the cytotoxic and cytolytic actions of HOCl.<sup>24</sup> Vermeulen et al reported a longer duration of mechanical ventilation and ICU support in critically ill patients with low plasma Taurine.<sup>25</sup> Low level of plasma Taurine was also reported in in critically ill septic<sup>26</sup> patients, and after trauma.<sup>27,28</sup> In this study, serum levels of IL-10 were measured on days 1 and 9 of admission. The first measurement showed higher values of cytokine, whereas the second measurement revealed a decrease. This was more noticeable in the Taurine supplemented group and demonstrates that this supplement can meliorates IL-10 level compared with the control group. Strongly decreased IL-10 levels by Taurine supplementation in brain injured rats was also shown by Su et al.<sup>29</sup> Furthermore, as a commonly used marker of acute inflammation,<sup>30</sup> the hs-CRP level reduction in the Taurine group shows faster control of the burn induced inflammation.

Patients in group T showed IL-10 levels that were significantly lower than of patients in control group ( $P < 0.05$ ). Furthermore, IL-10 level drop were significantly lower than the control group ( $P < 0.05$ ). Next we compared the hs-CRP and TNF- $\alpha$  profile in two groups (Table 2). There were no significant changes in serum concentrations of hs-CRP and TNF- $\alpha$  throughout the study period. Serum concentration did increase slightly although this change did not show statistical significance. Serum concentrations of these inflammatory markers are shown in Table 2.

Taurine is also suggested to be more effective in patients with a greater TBSA percentage, the stronger effect of the supplementation on patients with severe burns may be due to the presence of more inflammation and oxidative stress, and the subsequent need for more antioxidants and anti-inflammatory effects (Figure1). As more usage and decrease of antioxidants can be seen in injuries of greater severity or systemic inflammatory response syndrome.<sup>31,32</sup>



**Figure 1.** The Mean Difference of IL-10, hs-CRP, and TNF- $\alpha$  serum Level<sup>1</sup>  
<sup>1</sup>The mean difference of IL-10, hs-CRP and TNF- $\alpha$  serum levels are shown in days 1 and 9 of admission to hospital in both C (Control) and T (Taurine) groups. Group C is shown with a solid line whereas group T is shown with a dashed line. Mean average of measurements for TBSA percentage of <30% in each group are indicated with green color while the TBSA percentage  $\geq 30\%$  are indicated with color red.

Taurine is also suggested to be more effective in patients with a greater TBSA percentage, the stronger effect of the supplementation on patients with severe burns may be due to the presence of more inflammation and oxidative stress, and the subsequent need for more anti-oxidants and anti-inflammatory effects. As more usage and decrease of antioxidants can be seen in injuries of greater severity or systemic inflammatory response syndrome.<sup>27,28</sup>

After the first week of our study, there was less sepsis in the Taurine group than in the control group. However, the difference was not significant. All of our findings suggest that, Taurine supplement lowers inflammation.

On the basis of our present results, it is tempting to hypothesize that decreased levels of IL-10 may favor a benefit from a therapy with Taurine supplement. However, these preliminary data need to be confirmed with larger number of patient studies. The main limitations of this study were the low sample of patients followed by a short term of study. In order to obtain more accurate results, larger samples, more groups administered different doses of the supplement, and more frequent time interval measurements would help us to reach stronger conclusions.

### Conclusion

Despite improvements in the early care of burn, SIRS, MODS and severe sepsis remain major causes of mortality in burn patients. Most often, an inadequate nutrition leads to increased mortality. This study, regardless of the mechanism behind, clearly shows the benefit of Taurine supplement in burn injury patients especially the more severe ones by modifying the serum inflammatory cytokine levels. Further studies are required in order to identify the exact mechanism responsible for the efficacy of this nutritional supplement and the appropriate timing in order to determine if it should be administered to burn injury patients as a routine.

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### Ethical Issues

Informed consent was obtained from each patient (or their relatives). The study protocol was approved by the Ethics Committee of Tabriz University of Medical

Science (no. 91187) and registered in Iranian Registry of Clinical Trials (IRCT: no. IRCT201307082017N13).

No Other issues were applicable.

### Conflict of Interest

The authors report no conflicts of interest.

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