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ORIGINAL ARTICLE

The effect of levamisole on mortality rate among patients with severe burn injuries

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Background: Burn injuries are one of the main causes of mortality and morbidity throughout the world and burn patients have higher chances for infection due to their decreased immune resistance. Levamisole, as an immunomodulation agent, stimulates the immune response against infection. **Materials and Methods:** This randomized clinical trial was conducted in Motahari Burn Center, Tehran, Iran. Patients who had second- or third-degree burn with involvement of more than 50% of total body surface area (TBSA) were studied. The levamisole group received levamisole tablet, 100 mg per day. Meantime, both the levamisole and control groups received the standard therapy of the Burn Center, based on a standard protocol. Then, the outcome of the patients was evaluated. **Results:** 237 patients entered the study. After excluding 42 patients with inhalation injury, electrical and chemical burns, and the patients who died in the first 72 h, 195 patients remained in the study, including 110 patients in the control group and 85 in the treatment group. The mean age of all patients (between 13 to 64 years) was 33.29 ± 11.39 years (Mean ± SD), and it was 33.86 ± 11.45 years in the control group and 32.57 ± 11.32 years in the treatment group. The mean percentage of TBSA burn was 64.50 ± 14.34 and 68.58 ± 14.55 for the levamisole and control groups, respectively, with the range of 50-100% and 50-95% TBSA. The mortality rate was 68 (61.8%) patients in the control group and 50 (58.8%) patients in the treatment group ($P = 0.8$). **Conclusion:** According to this study, there was no significant relationship between improvement of mortality and levamisole consumption.

Key words: Burn, immunomodulation agent, infection, levamisole

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INTRODUCTION

Treatment of patients with extensive burns remains a major challenge, even with advances in burn care over recent decades.[1] Burn injuries are one of the main causes of mortality and morbidity throughout the world, and infections and inhalation injuries are the major causes of death following these injuries.[2-9]

Burns greater than 30% of the total body surface area (TBSA) particularly affect the immune system. Both the innate and adaptive, especially the cellular, immune systems are influenced by the thermal injury,[10-13] and effector mechanisms of nonspecific and specific host defenses are impaired (phagocytosis, chemotaxis, lymphocyte proliferation, antibody production).[14-19] Severe burn injury also alters the T cell by inducing an imbalance in T helper (Th) cell functions, caused by a phenotypic imbalance in the regulation of Th1 and Th2 immune response.[20-23]

Therefore, some ways have been developed to improve the immune response and host resistance to septic challenge in thermally injured patients. It has been indicated that consumption of polymyxin B and interleukin-2 can improve resistance against infections in the burned animal models.[24,25]

Levamisole is a derivative of levo isomer of tetramisole, a potent broad-spectrum anthelmintic.[26,27] In 1972, its immunomodulation effect was observed. It has been used in many clinical trials to treat many diseases including colon carcinomas, breast cancer, advanced malignant diseases, aphthous stomatitis, childhood nephrotic syndrome, chronic idiopathic urticarial, bacterial infections, and HIV infection with different results.[28-34] Levamisole stimulates the

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polymorpho-nuclear lymphocytes (PNL), macrophages, and T lymphocytes, and increases the chemotaxis and proliferation of these cells. Levamisole has an immunostimulant effect by proliferating natural killer cells, which kill T lymphocytes, virus-infected cells, and tumor cells.[24,30,35-39] Some studies have also shown that its consumption is almost effective in increasing immunity in burned human and animal models.[40-44]

Because of this modulatory effect of levamisole on immune system and the impairment of this system in burned patients, a study was designed to evaluate the effect of this drug on the mortality of severe second- and third-degree burns over 50% TBSA.

MATERIALS AND METHODS

This randomized parallel-group clinical trial study was conducted in Burn Center, Motahari Hospital, Iran University of Medical Sciences (IUMS), Iran from 7 July 2010 to 7 September 2011. The study was confirmed by the ethical committee of IUMS and was submitted in Iran clinical trial website (www.irct.ir). Written informed consent was obtained from all the participants (and/or their parents).

The study population included the patients who referred within 24 h of injuries with second- and/or third-degree thermal burns with more than 50% of TBSA. Patients with chemical burn, electrical burn, inhalation injury, underlying disease, and also the patients who expired within 72 h after hospitalization were excluded from the study. All of the admitted burn patients with 50% and more of TBSA who accepted to participate in the study were enrolled; thus, 237 patients entered the study. At the time of admission, they were randomly assigned to two groups of treatment and control. The levamisole group received levamisole tablet (Poorsina, Tehran, Iran) 100 mg/day until discharge from the hospital or death. Except this part of treatment, patients were treated separately based on their condition by surgeon's decisions.

Age, sex, etiology, percentage of the burned area, and outcome of each patient were registered.

The data were analyzed using the independent sample *t*-test, chi-square test, and analysis of variance (ANOVA) by means of SPSS software, with $P < 0.05$ considered as the level of significance.

RESULTS

From 7 July 2010 until 7 September 2011, 237 patients aged 13 years and over were enrolled in the study. Data were collected from 133 patients (78.9% males and 21.1% females) in the control group and 104 patients in the treatment group (76.9% males and 23.1% females).

The mean age of all patients (between 13 to 64 years) was 33.29 ± 11.39 years (Mean ± SD). It was 33.86 ± 11.45 years in the control group and 32.57 ± 11.32 years in the treatment group.

The major causes of burn were gas explosion (38%), flame (39.7%), self-immolation (17.3%), electrical burn (1.7%), and some others. All of them had second- and/or third-degree burn and more than 90% of them had head and neck, trunk, and extremities injury simultaneously.

After excluding 42 patients with inhalation injury, electrical and chemical burns, and the patients who died in the first 72 h, 195 patients remained in the study, including 110 patients in the control group (81.8% males and 18.2% females) and 85 in the treatment group (77.6% males and 22.4% females).

The mean percentage of TBSA burn was 64.50 ± 14.34 and 68.58 ± 14.55 for the levamisole and control groups, respectively, with the range of 50-100% and 50-95% TBSA.

Mortality among patients was 77 in the control group and 60 of the treatment group. There was no significant difference in mortality in the two groups ($P = 0.929$) [Table 1].

In both groups, mortality was significantly more common in female patients ($P = 0.009$ and 0.031, respectively), but mortality was not significantly different in males and females of levamisole and control groups ($P = 0.83$ and 0.61, respectively).

Levamisole had no effect in reducing mortality in subgroups of different ages (*P* value between 0.479 and 1) [Table 2].

Also, the mortality rate was not significantly different between the two groups at different percentages of burns (*P* value between 0.66 and 1) [Table 3].

Table 1: Mortality in levamisole and control groups

	Treatment group × death crosstabulation count			
	Death		Total	*P* value
	no	yes		
Treatment group				
control	33	77	110	0.929
levamisole	25	60	85	
Total	58	137	195	

Table 2: Mortality in age subgroups of levamisole and control patients

Age	Age group	Treatment group × death crosstabulation count: Death		Total	*P* value
		no	yes		
13-22.99	Treatment group				
	control	3	14	17	1
	levamisole	3	14	17	
	Total	6	28	34	
23-32.99	Treatment group				
	control	17	32	49	0.479
	levamisole	14	19	33	
	Total	31	51	82	
33-42.99	Treatment group				
	control	7	13	20	0.49
	levamisole	5	15	20	
	Total	12	28	40	
43-52.99	Treatment group				
	control	4	10	14	0.61
	levamisole	1	8	9	
	Total	5	18	23	
53 and more	Treatment group				
	control	2	7	9	1
	levamisole	2	4	6	
	Total	4	11	15	

Table 3: Mortality in different burn percentage of levamisole and control patients

TBSA (%)	TBSA group	Treatment group × death crosstabulation count: Death		Total	*P* value
		no	yes		
50-59.99	Treatment group				
	control	17	10	27	0.66
	levamisole	16	12	28	
	Total	33	22	55	
60-69.99	Treatment group				
	control	13	15	28	0.686
	levamisole	6	9	15	
	Total	19	24	43	
70-79.99	Treatment group				
	control	1	10	11	1
	levamisole	2	11	13	
	Total	3	21	24	
80-89.99	Treatment group				
	control	1	17	18	1
	levamisole	1	14	15	
	Total	2	31	33	
90-100	Treatment group				
	control	1	25	26	1
	levamisole	0	14	14	
	Total	1	39	40	

There were significant differences between the two groups in plasma transfusion ($P = 0.03$) and escharotomy surgery ($P = 0.04$). The transfusion and escharotomy indications and need were lower in levamisole group.

The differences in the debridement number ($P = 0.2$) and graft surgery ($P = 0.11$) were not significant.

DISCUSSION

Even with advances in burn care over recent decades, the treatment of patients with extensive burns remains a major challenge.[1,45] Recent data from the United States indicate 69% mortality among the patients with burns over 70% of TBSA.[45]

The immune system is altered after thermal injury. The severity of immune suppression correlates with the severity of injury. Depressed immune system is one of the major causes of the susceptibility of these patients to infection and sepsis. The humoral immunity is altered, as seen by the decreased levels of immunoglobulins, activation of complement, release of anaphylatoxins, and formation of membrane-attacking complexes. Also, the specific immune response is altered after burn, which includes a depressed ability to produce active rosette-forming cells, depressed stimulation of lymphocyte proliferation, as well as the mixed lymphocyte response. These effects are modulated by the release of kinins, prostaglandins, anaphylatoxins, superoxides, and leukotrienes, all of which can influence the inflammatory response following thermal injury. The immune response is also influenced by some drugs used for other reasons such as steroids, chemotherapeutic agents, and topical agents used for burn wound care.[46-48]

Any modulation that can improve the host defense mechanism has a beneficial effect on the rate of sepsis and infection and can decrease the mortality rate of burned patients. The study results of Stinnett *et al*. showed that immunomodulators could be of benefit in burns; however, not all agents are effective.[40]

Levamisole, a synthetic phenylimidazolthiazole, is a potent antihelmintic agent that was first introduced in 1966.[1,49]

After a few years, it was found that this drug had immunotropic properties and seemingly restored inefficient host defense mechanisms.[50]

In many clinical trials and experimental studies, it has been used as an immunomodulation agent for the treatment of cancers, viral and bacterial infections, and aphthous lesions. Moreover, there are many studies about the mechanism of its action over immune system.[1-3,6,9,18,51,52] It is also useful in the treatment of leprosy, based on an Indian clinical trial.[2,49]

Levamisole has been found effective in the improvement of immune system in some studies and had no effects in some other studies.

Niedworok *et al*. found that the survival time of the transplants was prolonged significantly by levamisole in healthy rabbits and was diminished in rabbits with burn disease.[42]

In a study on burned animals, it was found that continuous infusion of levamisole treatment significantly increased the inflammatory response.[41] The study by Matchin showed that levamisole, antioxidants, and hyperbaric oxygenation facilitated most rapid recovery of the immunological status in burned patients.[43]

In Stinnett *et al*.'s study in animal model, oral administration of levamisole did not reduce mortality in burned guinea pig, which was infected with *Pseudomonas* microorganism.[40]

The price of levamisole is low and has a few side effects if it is used for a short period of time. The plasma elimination half-life of levamisole is between 3 and 4 h. Levamisole is metabolized by the liver and the metabolites are excreted mainly by the kidneys (70% over 3 days). The elimination half-life of metabolite excretion is approximately 16 h, and 5% is excreted in the feces.[53]

The complications of levamisole include nausea, vomiting, fever, dizziness, headache, skin eruptions, mild anemia, and elevation of liver enzymes. Rare cases of side effects include agranulocytosis, thrombocytopenia, convulsion, and leukoencephalopathy. We did not evaluate the complications of the medication in our patients because the same complications are common in severely burned patients.[31,32,54-57]

This study indicated no significant relationship between mortality and improvement outcome with levamisole consumption in the patients with third-degree burn with more than 50% of TBSA. This meant that the levamisole group had an equivalent chance for improvement in comparison with the control group.

Our study has some limitations. First of all, we did not measure any immunological response such as immunoglobulin or immune cellular functions. We only evaluated the mortality as an index of better immunity of the patients and it is not enough.

Extensively burned patients were selected for this study. These patients had a high mortality rate and the immune modulation may be insufficient for reducing mortality in these patients. Also, the gastrointestinal absorption of the medication was not predictable in the victims of extensive burns and the blood level of levamisole was not measured.

Although this study showed no beneficial effect of levamisole in extensively burned patients, repetition of the study for less-extensively burned patients and evaluation of blood level of levamizole during the study can clarify the immunomodulation and infection-prevention effects of this medication in thermal injury.

CONCLUSION

Based on these findings, it can be suggested that levamisole consumption in second- and third-degree burn patients with the TBSA of more than 50% had no effect on mortality rate. It appears that more randomized trials with less-extensively burned patients are required to evaluate the exact blood level of levamisole in order to fully establish the efficacy of levamisole on the improvement and mortality rate of these patients.

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