



Pain Management by a Combination of Tramadol, Haloperidol and Carbamazepine in Iraqi Burn Patients

Waleed Ibraheem Ali^{1,2}, Eman Abdul Yemmah Hadi³, Zuhair A. Al-Johar^{2*}

¹ Head of Critical Care Unit, Ghazi Al-Hariri Teaching Hospital, Medical City, Baghdad, Iraq

² Department of Medicine, College of Medicine, University of Baghdad, Baghdad, Iraq

³ Burn Specialist Hospital, Medical City, Baghdad, Iraq

*Corresponding e-mail: zaljohar@comed.uobaghdad.edu.iq

ABSTRACT

Objectives: To study the effectiveness of the drug combination of haloperidol, carbamazepine, and tramadol for pain management in burn patients during a daily change of dressing for the first seven days of hospitalization. **Patients and methods:** Study was done on 30 burn patients (aged: 12-45 years) who were admitted to the burn specialist hospital, Medical city complex in Baghdad, Iraq from February 2016 to June 2016. In this study, we depended on using carbamazepine (given orally in a dose of 100- 200 mg twice per day) with haloperidol (0.05-0.15 mg/kg orally once daily) and tramadol (300 mg to 400 mg continues infusion for 12 hours). During the study, the pain was monitored by using a pain scale for adults and children, and behavior of patients was monitored by using an observational pain assessment scale. Vital parameters like pulse rate, systolic and diastolic blood pressure, duration of sleep for each patient were recorded on the first day of treatment with these drugs up till the seventh day. **Results:** Systolic and diastolic BP dropped by (95%CI: 9-21 mmHg; 4-13 mmHg respectively) and heart rate dropped by (95%CI: 25 to 37 b/min); duration of sleep increased to 6-7 hours per day in 19 patients (95%CI: 0.45-0.81). The median total pain score of 30 burn patients dropped from 9 to 1 over seven days; and 18 of 30 patients (95% CI: 0.4-0.75) became more calm, cooperative, relaxed, normal tone, no crying, and no negative response to wound touching. **Conclusions:** Tramadol infusion, oral haloperidol, and oral carbamazepine combination are effective in managing pain in burn patients.

Keywords: Tramadol, Haloperidol, Carbamazepine, Burn patients

INTRODUCTION

Pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage that is mediated via specific nerve fibers to the brain [1]. Pain is a subjective experience, no machine can measure pain, the only person who can determine the presence and degree of pain is the patient [2]. Training in appropriate pain assessment and the appropriate medication choices has been minimal for most healthcare providers [2]. Since pain is a subjective phenomenon then asking the patient directly is the only means by which clinicians can detect the existence of pain or quantify its severity. A useful means of assessing pain and evaluating the effectiveness of analgesia is to ask the patient to rate the degree of pain along with a numeric or visual pain scale as seen in Figure 1 [3,4]. Direct communication with the patient is the best method of determining comfort needs, not only that, it itself is a source of comfort to patients [5,6].

Drugs Used for Pain Control

Opioids: The agents most frequently used for pain relief and mild sedation. They are most effective for relieving dull pain, less effective for intermittent sharp pain and relatively ineffective for neuropathic pain [7,8]. Misconceptions about the addictive potential of opioids and about the appropriate dose needed to relieve pain had led to inadequate pain control especially in burn patients [9,10]. However, opioids use in hospitalized patients does not cause drug

addiction and the effective dose of opioids should be determined by patient response and not by some predetermined notion of what an effective dose should be [1].

Tramadol: It is a centrally acting analgesic that has opioid agonist activity and also has potent monoamine reuptake properties similar to many antidepressants so it seems to be valuable in the management of neuropathic pain [11].

Anticonvulsants: It is useful for patients with neuropathic pain as those agents block voltage-gated calcium or sodium channels thereby suppressing the spontaneous neural discharges and so they play a major role in managing neuropathic pain, which is less responsive to opioids than pain originating from nociceptors [2,12].

Carbamazepine: It is an anticonvulsant drug used to treat epilepsy and neuropathic pain [13]. It stabilizes the inactivated state of voltage-gated sodium channels and this leaves the affected cell less excitable until the drug dissociates. Carbamazepine is also a GABA receptor agonist. These mechanisms may contribute to its efficacy in neuropathic pain as well as in bipolar disorders [14].

Neuroleptics: It may occasionally be useful for patients with refractory neuropathic pain and may be most helpful in patients with marked agitation or psychotic symptoms [15].

Haloperidol: It is a neuroleptics drug and its therapeutic action appears to be due to blockade of dopaminergic receptors in mesolimbic sites [15]. However, the long duration of action makes it poorly suited for continuous infusion [16]. It doesn't carry any risk of cardiorespiratory depression and it is also effective in delirium [17].

Aim and Objectives

The aim of this study is to treat pain in burn patients to become more comfortable and cooperative with nursing staff during change dressing (a very stressful procedure which should be done daily) by the use of a combination of tramadol, carbamazepine, and haloperidol.

The objectives are to show the daily effects of using Tramadol, Carbamazepine, and Haloperidol during the first seven days on vital signs: systolic, diastolic blood pressures and pulse rate; duration of sleep; the severity of pain assessed by pain assessment scale; behavior of patients during change dressing assessed by observational pain scores.

PATIENTS AND METHODS

This is a prospective cohort study with a follow-up period of 7 days. Total 30 patients were admitted to the burn specialized hospital at Medical City Complex in Baghdad, Iraq from February 2016 to June 2016. The study was conducted in accordance with the declaration of Helsinki after approval from the authority of burn specialized hospital was taken.

Inclusion Criteria

Patients with age group 12- 45 years, percentage of burn 15%-40%, the degree of burn: deep 2nd and 3rd were included in the study.

Exclusion Criteria

Patients with a history of renal impairment, hepatic impairment, and hypertension were excluded in the study.

All patients in our study received Tramadol (Tramal) 200mg-300mg per day in 50 ml normal saline infused through a syringe pump at 5mg-10mg per hour for 12 hours. The dose was doubled at times of wound debridement and change dressing, Carbamazepine (Tegretol) 100mg-200mg p.o. q12h, Haloperidol (Haldol) (0.05-0.15 mg/kg (5mg-10mg p.o.) o.d. All patients were followed up for 7 days and monitored for pain by using: pain assessment scale which depends on the patient description of pain during a change of dressing and monitored for behavior by observational pain assessment scale (Table 1, Figure 1) [3,18].

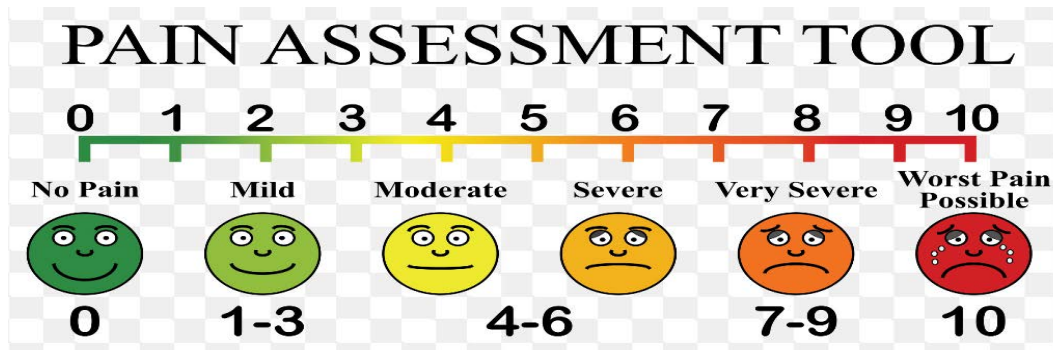


Figure 1 Pain Assessment Scale

Table 1 Observational pain assessment scale

Score	0	1	2
Restlessness	Calm, cooperative	Slight restlessness	Very restless, agitated
Muscle tension	Relaxed	Slight tenseness	Extreme tenseness
Facial expression	No frowning, or grimacing, composed	Slight frowning or grimacing	Constant frowning or grimacing
Vocalization	Normal tone, no sound	Groans moans, cries out in pain	Cries out, Shortness of breath
Wound guarding	No negative response to wound	Reaching gently touching the wound	Grabbing vigorously at the wound

Other parameters were monitored including blood pressure; pulse rate, and duration of sleep. Data were collected from the staff who changed dressing daily and those who monitor vitals and sleep. Data were then tabulated on paper, then entered electronically and analyzed by using SPSS-PC version 23.0. Descriptive analysis of the data using graphical and tabular analysis was conducted calculating the medians, means, and confidence intervals of each variable. The significance of differences between scalar variables was tested using paired Student’s t-test, while non-parametric data were tested using Wilcoxon signed rank matched pairs test when the differences were symmetric and the used sign test when the differences were asymmetric.

RESULTS

Blood pressure: Daily average systolic and diastolic blood pressure of 30 patients during the period of treatment was calculated (Figure 2).

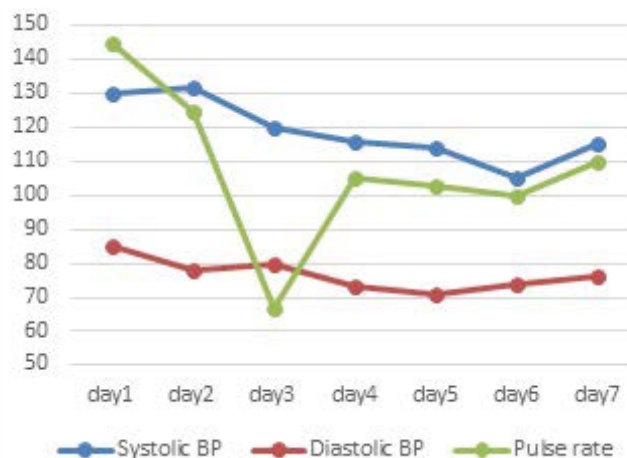


Figure 2 Hemodynamic status of 30 burn patients in the first seven days

Pulse rate: Daily average pulse rate for 30 patients during the period of treatment was calculated (Figure 2).

The significance of differences in pulse rate, systolic and diastolic blood pressures between the first and seventh day of treatment is shown in Table 2.

Table 2 Significance of differences in blood pressure and heart rate between the first and seventh day

Variable		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Systolic day1-Systolic day7	14.762	14.703	3.209	8.069	21.455	4.601	20	0.000
Pair 2	Diastolic day1-Diastolic day7	8.905	10.178	2.221	4.272	13.538	4.009	20	0.001
Pair 3	Heartrate day1-Heartrate day7	31.481	15.073	2.901	25.519	37.444	10.853	26	0.000

Duration of sleep increased to an average of 6-7 hours per day for 19 of 30 patients on the second day of treatment (mean: 0.63, 95% CI: 0.45-0.81).

Pain severity: Number of patients and their pain score during the seven days of treatment with tramadol, carbamazepine and haloperidol were measured (Table 3).

Table 3 Daily number of patients stratified by severity of pain

Variables	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Worst pain	17	0	0	0	0	0	0
Very severe pain	4	10	2	0	0	0	0
Sever pain	9	7	4	1	1	1	1
Moderate pain	0	7	12	15	15	12	12
Mild pain	0	6	9	5	5	4	5
No pain	0	0	3	9	9	13	12

The median total pain score of 30 burn patients dropped from 9 to 1 over seven days with consecutive daily drops occurring over the first four days after which drops occurred every other day (Figure 3, Table 4). The consecutive daily differences between the pain scores were found to be asymmetric. The sign test showed a significant drop in pain scores on all consecutive days before the sixth day, the exact 2-tailed significance using the binomial distribution showed a p-value of <0.39; the sign test also showed a significant drop between day 1 to day 7 (Z-test statistic -5.295, 2-tailed asymptotic significance of p=0.000).

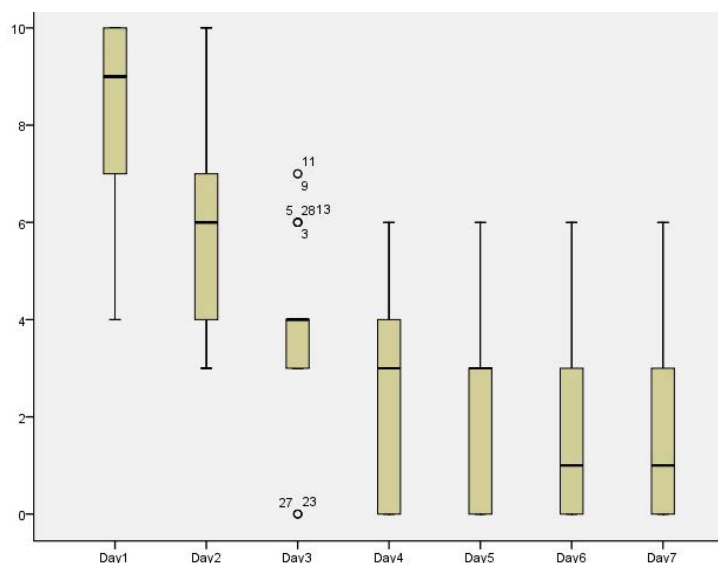


Figure 3 Box plots showing daily total pain scores in 30 burn patients over seven days

Table 4 Descriptive Statistics of total pain scores for 30 burn patients over seven days

Variables	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25 th	50 th (Median)	75 th
Day 1	30	8.3	1.968	4	10	6.75	9	10.0
Day 2	30	5.83	2.451	3	10	4.00	6	7.0
Day 3	30	3.77	1.813	0	7	3.00	4	4.5
Day 4	30	2.50	1.676	0	6	0.00	3	4.0
Day 5	30	2.07	1.639	0	6	0.00	3	3.0
Day 6	30	1.53	1.634	0	6	0.00	1	3.0
Day 7	30	1.57	1.612	0	6	0.00	1	3.0

Behavior of patients: According to an observational pain assessment scale, the behavior of patients during the seven days of treatment had extremely changed; 18 of 30 (mean 0.6, 95% CI: 0.43-0.75) of patients became more calm, cooperative, relaxed, normal sound tone, no crying, and no negative response to wound touching (Table 1). The median sum of all individual behavior scores of 30 burn patients dropped from 10 to 3 over seven days with consecutive daily drops occurring over the first 3 days after which drops occurred every other day (Table 5). The consecutive daily differences between the total behavior scores were symmetric for the first 3 days and asymmetric thereafter (Figure 4).

Table 5 Descriptive statistics: daily total behavior scores

Variables	N	Mean	Std. Deviation	Minimum	Maximum	Percentiles		
						25 th	50 th (Median)	75 th
Day 1	30	9.43	1.104	6	10	9.00	10	10
Day 2	30	7.03	1.752	4	10	6.00	7	8
Day 3	30	5.23	1.612	2	10	4.75	5	6
Day 4	30	4.27	1.617	0	7	3.75	5	5
Day 5	30	3.53	1.408	0	6	3.00	4	4
Day 6	30	3.3	1.466	0	5	2.75	4	4
Day 7	30	2.7	0.535	0	5	1.75	3	4

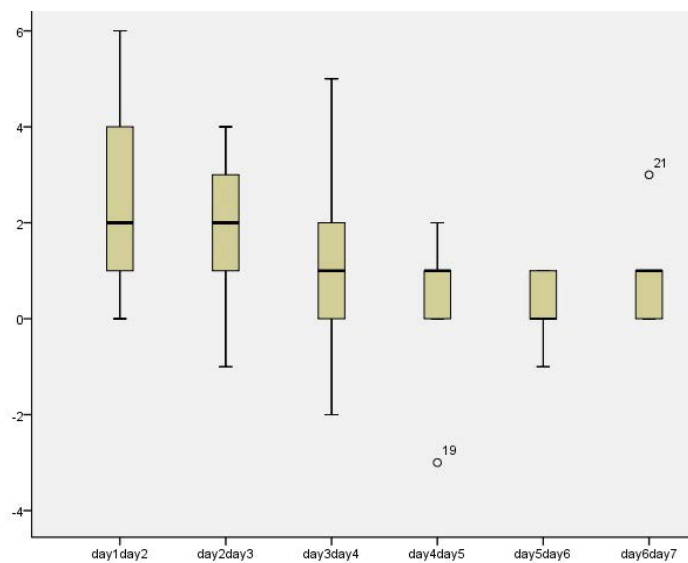


Figure 4 Box plots of consecutive daily differences in total behavior scores for 30 burn patients

The Wilcoxon and sign test showed significant drop in pain scores on all consecutive days of the first week [Z-test statistic (based on positive ranks): -4.411(1st-2nd day), -4.552(2nd -3rd day), -3.270(3rd-4th day), -3.439(4th-5th day),

-2.333(5th-6th day), -3.900(6th-7th day); 2-tailed asymptotic significance: $p=0.000, 0.000, 0.001, 0.001, 0.02, 0.000$, respectively]. The sign test showed similar results [2-tailed exact significance (binomial distribution used): $p=0.000$ (1st-2nd day), 0.000 (3rd-4th day), 0.000 (4th-5th day), 0.039 (5th-6th day), 0.000 (6th-7th day); Z-test statistic -4.725 (2nd -3rd day), 2-tailed asymptotic significance of $p=0.000$].

DISCUSSION

During the course of the acute phase of injury, burn patients must endure numerous painful procedures that produce intense physical and psychic stress, including initial wound debridement, daily dressing changes, exercise therapy and placement of intravascular catheters. For a number of reasons, adequate control of the pain and anxiety associated with these procedures is especially challenging due to multiple factors such as it is an intense but brief pain; risk of complications with deep sedation; prolonged effects of deep sedation; frequent fasting periods disrupt nutritional needs of burn patients; controversy over who should administer deep sedation. Poorly controlled pain can make it difficult to accomplish an effective or safe procedure and increase anticipatory anxiety can impair the patient's compliance and may contribute to behavioral morbidity such as post-traumatic stress syndrome, also it may increase sympathetic tone; on the other hand, impaired wound healing and immune function are associated with pain and can contribute to prolonged hospitalization [18]. Because pain can be affected by past experiences, suggestion, emotion (particularly anxiety) and simultaneous activation of other sensory modalities, thus the level of pain experienced is not solely a physical property of the stimulus [19]. Rest and sleep help the body to maintain homeostasis, restores energy level and decrease stress and anxiety [20].

This is the first time a research is conducted using this drug combination to treat pain in burn patients, the use of the individual drugs in burn patients had been tried before [21,22]. The current research supports the viewpoint of treating pain with multiple drugs (multimodal balanced analgesia), the sample size of the current study is relatively small that comparisons with other studies can't be confidently drawn. However, it does point towards favoring this kind of drug combination which gave positive results in all patients on all 4 targets of the study:

Vital signs: The average change in systolic blood pressure showed a significant decrease in the first 3 days of treatment and after that it reached approximately constant level from day 4 to day 7; the average change in diastolic blood pressure showed a gradual decrease in the first three days of treatment and then reached constant level from day 4 to day 7. The average change in pulse rate showed marked a decrease from 140 b/min in the first day to 60 b/min in the third day reaching a constant level in the last 4 days of treatment between 100-110 b/min (Figure 1). We believe that this came as a response to the decrease in severity of pain and related stress as a result of the treatment with our drug combination.

Duration of sleep: The duration of sleep increased to 6-7 hours per day for 19/30 of the patients on the second day of treatment and their sleep were deep and comfortable. We believe that it came as a response to decrease in severity of pain and related stress as a result of the treatment with our drug combination.

Severity of pain: Total pain scores showed drops on daily basis this involved both background pain and procedural pain (Figure 3, Table 4). Despite asymmetry of the consecutive daily differences in total pain scores, the sign test showed them all to be statistically significant; the drop was also clinically significant dropping from 9 to 1 on total pain score from day 1 to day 7. This drop is mostly related to the effect of the drug combination used. It is not generally expected for deep 2nd degree or 3rd degree burn pain to decrease down to such an extent without any medications. Patients with burn have increased levels of anxiety especially related to treatment and that these levels may increase over time, the anticipation of pain related to wound care that occurs at least daily can increase a patients perception of pain which in turn can lead to greater anxiety. This reaction may explain the need for analgesia with daily change dressing in burns. Depression also plays a similar role in the enhancement of pain. Pain leads to depression and depression enhances the perception of pain [18].

Behavior of patients: Results showed that 18 patients became calmer and cooperative, relaxed, easier to touch and deal with their wound from the 2nd day of treatment. Results about the daily sum of all observation pain behavior scores in our patients showed that the sum of all behavior scores dropped significantly in the period of study on daily basis and then on every other day basis (Figure 4, Table 5). For although this sum score is not usually used in clinical practice it does give an impression here of the overall behavior status of the patients, all results were statistically significant. All of this supports a positive effect on behavior in burn patients in the first seven days of treatment,

which is not the usual experience with deep 2nd and 3rd degree burn patients, many of which have hard times at procedures like a daily change of dressing and other procedures. Daily cleaning of the wound, topical applications, and occlusive dressings remain the preferred recommended management technique especially for injuries where sufficient epidermal living cells remain to ensure a degree of satisfactory spontaneous healing [23]. It is essential to recognize the significance of the clinical technique used in the first dressing which is usually applied on admission since inadequate pain management at this stage will have a lasting effect as the patient may dread subsequent dressing change and lose confidence in the care team as the post dressing background pain intensity is always greater than the pain experienced before dressing change [24]. Non-compliance with hospital treatment disrupted care and increased risk of post-traumatic stress disorders are all known to result from inadequate treatment of pain in burn patients [25].

Although the problem of undertreated burn injury pain was well described more than 20 years ago and despite a call to make pain the highest research priority in burn care due to its detrimental effects on patients as well as those who care for them more than 15 years ago, burn injury pain remains a continuing challenge. Recent publications report unacceptably high pain ratings (mean: 7/10). This is disconcerting when one considers the wide availability of pain management guidelines and the promotion of guideline-based treatment approaches. In addition to that, unlike surgical pain that subsides gradually, burn injury pain is highly variable and may increase over time, much to the patient's distress, before healing is accomplished. This makes approaching burn injury pain with the World Health Organization's analgesic ladder or titrating to affect often impractical. These factors trigger us to establish our own protocol in our burn unit to solve this problem with these effective, cheap and available drugs.

CONCLUSION

Treatment with tramadol infusion in combination with carbamazepine and haloperidol orally is effective in managing background pain as well as in decreasing stress and anxiety in burn patients during daily change dressing and debridement which is a very painful and stressful procedure. It is effective during the first seven days of burn in achieving hemodynamic stability, increasing the duration of sleep, decreasing pain severity and improving behavior.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

- [1] Stedman, Thomas Lathrop, ed. *Stedman's medical dictionary for the health professions and nursing*. Lippincott Williams and Wilkins, 2005.
- [2] Duke, Ames. *Anesthesia secrets*. Elsevier Health Sciences, 2006.
- [3] McPhee, Stephen J., et al. *Current medical diagnosis and treatment 2010*. New York: McGraw-Hill Medical, 2010.
- [4] Hockenberry, Marilyn J., David Wilson, and Cheryl C. Rodgers. *Wong's Essentials of Pediatric Nursing-E-Book*. Elsevier Health Sciences, 2016.
- [5] Murray, MJ and Plevak, DJ. "Analgesia in critically ill patients." Rochester, Mayo medical center 1994,2:56_63.
- [6] Hamill-Ruth, Robin J., and M. Lynn Marohn. "Evaluation of pain in the critically ill patient." *Critical care Clinics*, Vol. 15, No. 1, 1999, pp. 35-54.
- [7] Dasta, Joseph F., Thomas M. Fuhrman, and Cynthia McCandles. "Patterns of prescribing and administering drugs for agitation and pain in patients in a surgical intensive care unit." *Critical Care Medicine*, Vol. 22, No. 6, 1994, pp. 974-80.
- [8] Soliman, H. M., Christian Mélot, and J□L. Vincent. "Sedative and analgesic practice in the intensive care unit: the results of a European survey." *British Journal of Anaesthesia*, Vol. 87, No. 2, 2001, pp. 186-92.
- [9] Melzack, Ronald. "The tragedy of needless pain." *Scientific American*, Vol. 262, No. 2, 1990, pp. 27-33.
- [10] Zenz, M., and A. Willweber-Strumf. "Opiophobia and cancer pain in Europe." *The Lancet*, Vol. 341, No. 8852, 1993, pp. 1075-76.

-
- [11] Walker, Roger. *Clinical Pharmacy and Therapeutics E-Book*. Elsevier Health Sciences, 2011.
- [12] Bridges, D., S. W. N. Thompson, and A. S. C. Rice. "Mechanisms of neuropathic pain." *British Journal of Anaesthesia*, Vol. 87, No. 1, 2001, pp. 12-26.
- [13] Steven, M Yentis and Nicholas, Phirsch. "*Anaesthesia and intensive care*." Canada.
- [14] Kawata, Yuko, et al. "Pharmacological discrimination between effects of carbamazepine on hippocampal basal, Ca²⁺ and K⁺ evoked serotonin release." *British Journal of Pharmacology*, Vol. 133, No. 4, 2001, pp. 557-67.
- [15] Morgan, G. Edward, et al. *Clinical Anesthesiology*. New York: McGraw-hill, 2002.
- [16] Riker, Richard R., GILLES L. Fraser, and Paul M. Cox. "Continuous infusion of haloperidol controls agitation in critically ill patients." *Critical Care Medicine*, Vol. 22, No. 3, 1994, pp. 433-40.
- [17] Marino, Paul L., and Kenneth M. Sutin. *The ICU book*. Vol. 2. Baltimore: Williams and Wilkins, 1998.
- [18] David N. Herndon. *Total burn care*. Elsevier Health Sciences, 2007.
- [19] Vander, Arthur J., et al. *Human physiology: the mechanisms of body function*. Boston: McGraw-Hill, 1998.
- [20] Taylor, Carol, et al. "Fundamentals of nursing." *The art and science of nursing care*, 1990.
- [21] Ratcliff, Stephen L., et al. "The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient." *Burns*, Vol. 32, No. 5, 2006, pp. 554-62.
- [22] Choinière, Manon, et al. "The pain of burns: characteristics and correlates." *The Journal of Trauma*, Vol. 29, No. 11, 1989, pp. 1531-39.
- [23] Atchison, Nancy E., et al. "Pain during burn dressing change in children: relationship to burn area, depth and analgesic regimens." *Pain*, Vol. 47, No. 1, 1991, pp. 41-45.
- [24] Andreasen, N. J., et al. "Management of emotional reactions in seriously burned adults." *The New England Journal of Medicine*, 1972.
- [25] Summer, Gretchen J., et al. "Burn injury pain: the continuing challenge." *The Journal of Pain*, Vol. 8, No. 7, 2007, pp. 533-48.