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Research Article

The Effect of Analgesia with Ketamine, Morphine and Paracetamol for Burn Pain in North-Eastern Iran

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ABSTRACT

Background: Pain is a common and challenging problem in burn patients. The severity of pain in these patients often requires multi drug therapy. On the other hand, with increasing the number and dosage of drugs, the complications increase, so finding an instruction that provides acceptable analgesia with minimal complications is necessary.

Methods: Based on the dose and half-life, the initial dose for paracetamol was 15 mg/kg every 6 hours, this dose was reduced to 30% after three days of initiation of the treatment to prevent liver toxicity and was discontinued after one week. Morphine started with an initial dose of 0.01 mg/kg/h and for opioid-tolerant patients, the initial dose was 0.02 mg/kg/h. Morphine infusion dose raised by 30 percent every week. The continuous intravenous infusion of ketamine (0.15 mg/kg/hr) with continuous intravenous infusion of morphine was administered by a silicone pump.

Results: The mean NRS was significantly reduced in the first visit after the intervention (three hours later) (8.5 ± 1.04 vs.3.9 ± 1.74; $p < 0.001$) and this decrease was observed in NRS in continuous observations ($P > 0.001$). Pain reduction was independent of history of opioids use.

Conclusion: Continuous infusion of ketamine, morphine and paracetamol showed an effective pain management program for burn patients.

Pain is a common and challenging problem in burn patients. The wide area of the skin, which is the largest organ in the body, contains the most sensory and pain receptors in comparison with other organs, and as a result, burned patients often experience a lot of pain at the burning surface. On the other hand, acute pain can cause central sensitization and stress response that can increase complications, morbidity and mortality.

The severity of pain in patients with burns and the nature of pain, which is often nociceptive and neuropathic, leads to the need for multidrug therapy. On the other hand, complications increase with rising in the number and dosage of pain medications and therefore it is necessary to find a protocol that provides acceptable analgesia with minimal complications.

Pharmacotherapies for pain control in burns include opioids, nonopioid analgesics, anxiolytics and some anesthetic drugs.

In the study of Askay et al., opioids have been mentioned as the most effective pain control drug in burn patients, which have a significant role in reducing the

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stress of these patients due to the effect of dose-dependent sedation [1]. Abdi S and Zhou Y in another study showed that the use of opiates in burns does not increase the dependency on the drug [2].

Another study showed that patient-control analgesia (PCA) with intravenous opiates can effectively control burn pain [3]. Nonopioid drugs such as dexmedetomidine and ketamine, also provide sedation and short-term analgesia for debridement or dress changing inside or outside of the operating room. Ketamine with clonidine provided acceptable analgesia for dressing replacement of children with severe burns [4-5].

Other non-opioid analgesics, such as NSAIDs and acetaminophen, are suitable for mild to moderate pain and patients who are being discharged [6].

Anxiety is a common side effect of burns and this anxiety is exacerbated by painful operations. In addition, anxiety increases the amount of pain. For this reason, anti-anxiety drugs have been added to the opium diet over the past three decades [7].

In a study on 79 burn patients, adding 1 mg of lorazepam to an opioid regime showed a significant decrease in pain in comparison with a placebo [8].

Antipsychotic drugs are also used to treat anxiety and restlessness caused by pain in burn patients [9]. Nitrous oxide also provides acceptable analgesia with sedation while keeping alertness. 50 % Mixture of nitrous oxide in oxygen can be delivered via a face mask [10-12].

In the intensive care unit, it is possible to carry out small operations such as dressing changes with short-acting anesthetics like Propofol and Sevoflurane [13-14]. A combination of Ketamine or tramadol with Acetaminophen for acute pain control has been studied with better results for postoperative analgesia and agitation score with Ketamine and Paracetamol [15].

Regarding the previous studies on the effectiveness of pain control drugs for burn patients, it was decided to use a continuous infusion of morphine, ketamine and paracetamol. Ketamine is a strong analgesic drug that blocks the NMDA receptors so can prevent chronic pain and central sensitization. Moreover, it has sedative properties which is a needed treatment for many burn patients [16-17]. Paracetamol is an effective analgesic with a central dominant effect on 5-HT receptors [18]. Morphine with the block of μ and k-opioid receptors in the central and peripheral nervous system prevents the transmission of pain messages by these receptors [18-19].

This study was designed to evaluate combined analgesia therapy with intravenous continuous infusion of morphine and ketamine with paracetamol for admitted burn patients.

Methods

This Quasi-Experimental study was performed on burn patients referred to the burn section of Imam Reza Hospital in Mashhad in 2017. Imam Reza Hospital is a referral hospital for burn patients in Iran.

According to Bamshcki et al. Study [20] and considering pain as the main outcome in determining the sample size with errors $\alpha = 0.05$ and $\beta = 0/1$, the sample size was calculated with SPSS23 and 32 patients enrolled in the study.

A pilot study based on the doses of the drug in the previous studies was designed and performed and we had to change just the ketamine dose from 0.3 mg/kg/h dose in the previous study to 0.15 mg/kg/h because the first recommended dose accompanied with severe drowsiness interfered with the cooperative patient needed for routine daily dressing change [16].

The primary dose for paracetamol (Tylophen®, ExirIran) was 15 mg/kg every 6 hours, which was infused IV with 100 ml of normal saline over 15 minutes. To prevent liver toxicity after three days, the dose decreased to 10 mg per kilogram body weight every 6 hours and stopped after one week.

The primary dose of morphine (Iran's Distribution Drug Company) was 0.01 mg/ kg/h which was doubled for patients with a history of opium abuse and started with 0.02mg/kg/h. Continuous IV infusions for Ketamine (Rotexme Germany) were 0.15 mg/kg/hr. which is infused accompanied with Morphine in 100 ml of normal saline by a silicone pump (Zhejiang, Fert Medical, China).

The presence of other concomitant illnesses or non-opioid drug abuse was a measure of withdrawal from the study.

32 patients with second or third-degree burns admitted in the burn ward with a pain score of 3 or more on the NRS scale were enrolled in this study. NRS scores, vital signs and complications were recorded for 30 patients.

The patient's pain was measured by an anesthesia nurse before starting the infusion, three hours later and then every eight hours. In the event of complications such as nausea or drowsiness that interfere with consciousness or nutrition, the drug infusion was discontinued for two hours, and then the infusion was continued with a 30 percent reduction in the drug doses. The duration of the treatment was recorded for each patient until discharge or death.

In the burn, section morphine was typically prescribed intermittently as PRN order but in this study, the drugs were prescribed continuously by IV administration.

Two patients were excluded due to excessive drowsiness, one patient on the second day and one patient on the fourth day of the study were excluded because of drug intolerance and lack of cooperation for a dressing change. Other patients did not experience a significant reduction in the level of consciousness or Vital signs problems.

Statistical analysis

Data from clinical and demographic observations were analyzed using SPSS version 23 software. The characteristics of the studied variables were described by

the central indexes of dispersion and frequency distribution, and repeated measurements were used to compare pain severity before intervention and for sequential follow up. In all analyzes p <0.05 was considered as a significant level.

Results

In this study, 32 patients were enrolled during the period from May to March 2017 and intervention was continued for 30 patients until discharge or death. Patients included 17 women and 13 men and the mean age of patients was 29.4± 11.13. In this study, the minimum age was 16 years and the maximum age was 62 years. The mean burn percentage was 43.4 ± 26.4 and the lowest and highest percentages of burns were 18 and 100, respectively.

Comparison of pain severity before and after drug combination with the Friedman test showed a significant decrease with P value <0.001.

The mean of pain before the intervention in the population was 8.5 ±1.04. In the first observation after the intervention (3 hours later), the pain was significantly decreased (p <0.001), and the pain severity for all measurements significantly decreased (p <0.001)

(Figure 1).

5 patients died during the study. The burn percentage of the deceased patients was higher than the rest of the patients in the study. (28.59 ±8 vs. 84.25 ± 11.38; P = 0.28). The severity of pain at the beginning of admission in the deceased patients (9.6 ± 0.54) was significantly higher than that of the discharged patients (8.17 ± 0.98) (P<0.001). However, pain intensity after intervention in patients before dye also significantly decreased (P<0.001). Pain reduction for patients who were discharged or died did not a show significant difference (Figure 2).

Also, significant pain relief was observed in opioid abusers (P<0.001) (Figure 3).

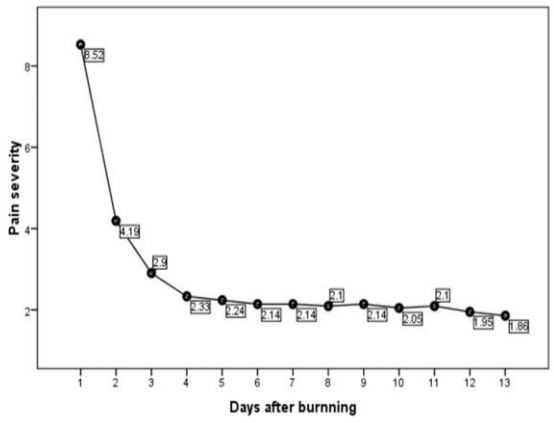

Figure 1- Changes in pain severity after admission and subsequent therapeutic intervention. The severity of pain has decreased over time after admission. Data are mean±SD (n=7). P< 0.001

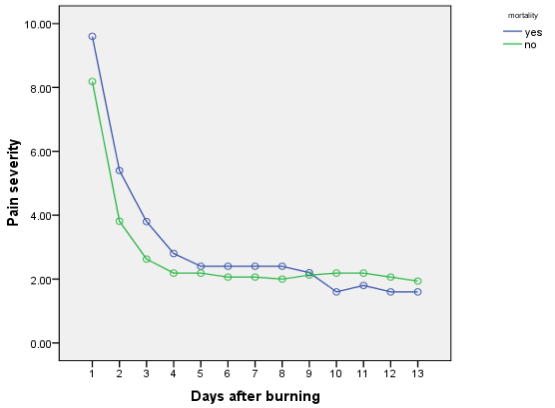

Figure 2- Comparison of changes in pain severity after admission and subsequent therapeutic intervention between patients who survived and those who died. Data are mean±SD (n=7). P< 0.001.

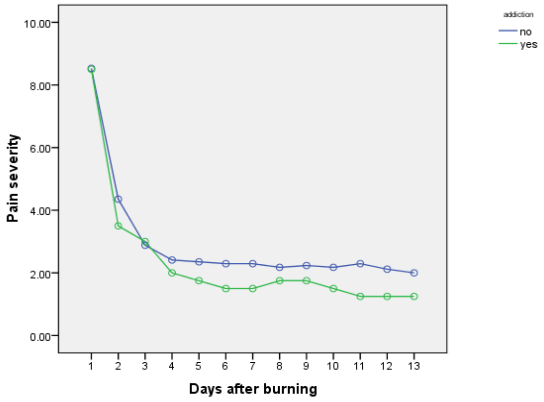

Figure 3- Comparison of changes in pain severity after admission and subsequent therapeutic intervention between opioid abusers and non-abuser patients data are mean±SD (n=7). P< 0.001.

Discussion

In this study, Combination therapy of the three drugs of Ketamine, Paracetamol and Morphine was evaluated for burn pain control.

The trend of pain changes between different individuals was compared based on gender, the extent of burns, opioid dependence, and overall outcome (death).

The trend of pain changes in women and men was decreasing and there was no significant difference in terms of pain reduction between opioid-tolerant and non-opioid-tolerant patients.

Bameshki et al showed oral Ketamine is effective for burn pain control regardless of age, gender and percentage of burn injury [21].

Ostadalipour et al evaluated the analgesic effect of clonidine which can be added to burn pain control regimes with some cautions [22].

In the study of combination therapy with morphine and clonidine by Lyons et al. addition of clonidine improved psychological, gastrointestinal, and ventilatory function by reducing morphine consumption. In the present study, due to the concomitant use of ketamine and paracetamol with morphine, the dose of morphine used did not cause any specific ventilatory or gastrointestinal problems in patients [5].

In our study, after starting the combination drugs therapy all patients with different extents of burns and pain intensity, pain scores decreased in all measurements.

Comparing the combination of these drugs therapy with different doses and other pain control regimens and also with a larger sample size is recommended.

Conclusion

Pain in patients with any prognosis was reduced. Continuous infusion of ketamine, morphine and paracetamol was associated with a significant reduction in the burn pain.

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References

[1] Wiechman Askay S, Patterson DR, Sharar SR, Mason S, Faber B. Pain management in patients with burn injuries. Int Rev Psychiatry. 2009; 21(6):522-30.

[2] Abdi S, Zhou Y. Management of pain after burn injury. Curr Opin Anaesthesiol, 2002; 15:563.

[3] Sharar SR, Carrougher GJ, Selzer K, O'Donnell F, Vavilala MS, Lee LA. A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. J Burn Care Rehabil. 2002; 23(1):27-31.

[4] Kariya N, Shindoh M, Nishi S, Yukioka H, Asada A. Oral clonidine for sedation and analgesia in a burn patient. J Clin Anesth. 1998; 10(6):514-7.

[5] Lyons B, Casey W, Doherty P, McHugh M, Moore KP. Pain relief with low-dose intravenous clonidine in a child with severe burns. Intensive Care Med. 1996; 22(3):249-51.

[6] Richardson P, Mustard L. The management of pain in the burns unit. Burns. 2009; 35:921.

[7] Martin-Herz SP, Patterson DR, Honari S, Gibbons J, Gibran N, Heimbach DM. Pediatric pain control practices of North American Burn Centers. J Burn Care Rehabil. 2003; 24(1):26-36.

[8] Patterson DR, Ptacek JT, Carrougher GJ, Sharar SR. Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. Pain. 1997; 72:367.

[9] Vulink N, Figee M, Denys D. Review of atypical antipsychotics in anxiety. EurNeuropsychopharmacol. 2011; 21:429-49.

[10] Richardson P, Mustard L. The management of pain in the burns unit. Burns. 2009; 35:921-36.

[11] Filkins SA, Cosgrav P, Marvin JA. Self-administered anesthesia: A method of pain control. J Burn Care Rehabil, 1981; 2:33.

[12] Yuxiang L, Lu T, Jianqiang Y, Xiuying D, Wanfang Z, Wannian Z, et al. Analgesia effect of a fixed nitrous oxide/oxygen mixture on burn dressing pain: study protocol for a randomized controlled trial, Trials. 2012; 13:67.

[13] Dimick P, Helvig E, Heimbach D, et al. Anesthesia-assisted procedures in a burn intensive care unit procedure room: benefits and complications. J Burn Care Rehabil, 1993; 14:446-9.

[14] Powers P, Cruse C, Daniels S, Stevens B. Safety and efficacy of debridement under anesthesia in patients with burns. J Burn Care Rehabil,1993; 14:176-80.

[15] Khajavi MR, Sabouri SM, ShariatMoharari R, Pourfakhr P, Najafi A, Etezadi F, et al. Multimodal Analgesia with Ketamine or Tramadol in Combination With Intravenous Paracetamol After Renal Surgery. Nephrourol Mon. 2016; 8(4).

[16] McGuinness SK, Wasiak J, Cleland H, Symons J, Hogan L, Hucker T, et al. A systematic review of ketamine as an analgesic agent in adult burn injuries. Pain Med. 2011; 12(10):1551-8.

[17] Schulte H, Sollevi A, Segerdahl M. The synergistic effect of combined treatment with systemic ketamine andmorphine on experimentally induced windup-like pain in humans. AnesthAnalg. 2004; 98(6):1574-80

[18] Gregoretti C, Decaroli D, Piacevoli Q. Analgo-Sedation of Patients with Burns Outside the Operating Room. Drugs. 2008; 68 (17): 2427-2443.

[19] Miller R, Cohen N, Miller's Anesthesia, eight's edition, Philadelphia; Elsevier Sanders,2015:ch 98,p 2977, table 98-1.

[20] Bameshki A, Mirhoseini M, Jahanbakhsh S, Soltani G, (Persian). Effects of oral ketamine on pain severity in burn patient. Anaesthesia and critical care 2005; 2(50).

[21] Bameshki AR, Mirhosseini ME, Jahanbash S, Soltani G. Evaluation of oral ketamine for postoperative pain in burn patients. J Anesthesiology and ICU care. 2005; 50 (2):30-35.

[22] Ostadalipour A, Jamshidi M, Zamani A, Jamshidi M, Ashrafi Tavasoli A. Analgesic and antisympathetic effects of clonidine in burn patients, a randomized, double-blind, placebo-controlled clinical trial. IJPS. 2007; 40 (1):29-33.