Nitrous Oxide-Oxygen Mixture During Burn Wound Dressing: A Double-Blind Randomized Controlled Study

Yu-Xiang Li,^{1,2} Wen-Jun Han,¹ Hong-Tai Tang,³ Yin-Sheng Wu,⁴ Lu Tang,¹ Jian-Qiang Yu,² Yan-Cang Li,⁵ Zhao-Fan Xia³ & Ji-Jun Zhao¹

¹ Department of Nursing, Changhai Hospital, Second Military Medical University, Shanghai, China

² Ningxia Medical University, Yinchuan, China

³ Burns and Trauma Centre, Changhai Hospital, Second Military Medical University, Shanghai, China

⁴ Burns and Plastic Surgery of the Affiliated Hospital of Ningxia Medical University, Yinchuan, China

⁵ Burn Centre, the First People's Hospital of Zhengzhou, Zhengzhou, China

Correspondence

Ji-Jun Zhao, No. 168 Changhai Road, Shanghai, 200433, China.

Tel.: 86-21-8187-3176;

Fax: 86-21-6549-2727;

E-mail: li_yuxiang@163.com

Received 23 November 2012; revision 30

December 2012; accepted 30 December

2012.

doi: 10.1111/cns.12061

The first two authors contributed equally to this work.

In China, there are 5–10 million burns victims each year [1]. Painful procedures are frequently required during treatment of burns wounds. Uncontrolled burns dressing pain induced anxiety and reluctance by patients to participate in their wound care and rehabilitation and is difficult to predict from wounds [2]. Previous studies have shown that pain suffered by burns survivors during dressing change is untreated and poorly managed due to the fear of adverse effects of opioids analgesics in both physicians and patients, lack of burns pain management guidelines, and the assistance of an anesthetist. Some healthcare providers in burns centers are also troubled by the dilemma of side-effects of opioids analgesics and patients' rights to freedom from pain. They stated their willingness to control burns dressing pain [3,4]. However, dressing change analgesia is a difficult problem because of the requirements of intense, but short-duration analgesia [5,6].

An equimolar nitrous oxide and oxygen mixture (NOOM) inhalation, available as a portable gas cylinder, has a rapid effect that ceases immediately when not in use. The mixture leads to conscious sedation, that is, analgesia without anesthesia and is tranquilizing. The absorption and elimination by the pulmonary route are very quick, and this results in a very rapid clinical effect. The drug has a low solubility in blood and tissues. The time to obtain the medium of the saturation level is 5 min, and 5 h is required for total saturation [7]. It is unlike the operator-titrated 70% maximum nitrous oxide/oxygen mixture delivered by a continuous flow system in Zier et al.'s study [8,9]. The latter requires specialist training and machinery that is not typically available in the

burns dressing setting. NOOM has been used for a long time in pediatric, obstetric, and emergency services to provide analgesia during brief, painful procedures. The feasibility, effectiveness, and safety of use in burns dressing pain management have not been studied.

This study aims to test the safety and analgesic effect of NOOM to define its place in the analgesic strategy during burns wounds dressing.

Patient eligibility, recruitment, consent, and randomization was previously reported [4]. The ethical approval from the Hospital Ethics Committee (CHEC2011-105) of each participating burns center was obtained. In total, 240 patients (male, $n = 128$; female, $n = 112$) aged sixteen to sixty-five (mean age 30.3 ± 12.8) who were eligible for inclusion were enrolled in the study. They were randomly assigned to receive the usual pain treatment+oxygen (UTO, $n = 60$) and usual pain treatment +NOOM intervention (UTN, $n = 180$), respectively, 2 min before dressing, based on the current clinical practice, from October 2011 to September 2012.

For each group, primary outcomes include:

- 1 Pain severity (VAS) during dressing measured as the mean of average and worst pain and
- 2 Burns dressing induced anxiety recorded on the Chinese version Burns Specific Pain Anxiety Scale (C-BSPAS) [10].

Physiological parameters including blood pressure (BP), heart rate (HR), digital oxygen saturation (SpO_2), and acceptance of both health care providers' and patients' were considered as sec-

ondary outcomes. All these parameters were taken 2 min prior to intervention, during dressing, immediately after dressing and 10 min after dressing. A video and audio record were taken individually for later communication, coding, and outcome analysis. Other characteristics including sex, age, and total burn area of body surface (TBSA) were recorded as well. Rescue analgesic was recorded.

SPSS 17.0 was used for statistical analysis. Comparison for baseline characteristics between two sets of patients was performed with ANOVA for continuous parameters followed by univariate analyses for analyzing the results of VAS, C-BSPAS, and physiological parameters. Mann–Whitney analysis was used for acceptance and Chi-Square test for age, sex. A *P* value of less than 0.05 was considered statistically significant.

In this study, pain severity was assessed with VAS (visual analog scale [zero to ten] on the Changhai Pain Scale, where zero stands for no pain and ten for unbearable pain. The scale chosen for pain assessment was categorized as mild [VAS 0 to 4.0], moderate [VAS 4.1 to 6.0], and severe [VAS > 6.0]). Analysis of pain severity (VAS) during dressing demonstrated a significant decrease in NOOM-treated patients with 1.65 ± 1.34 versus 9.39 ± 0.74 in controls ($P < 0.01$).

Given that the acute pain from burns dressing change induces anxiety [8], the anxiolytic effect of NOOM was assessed by evaluating patients' psychological reactions with C-BSPAS (zero to one hundred) where zero represents not at all and one hundred exactly agrees for each of the following five items focusing on dressing pain related anxiety.

- 1 I find it impossible to relax when my burns are being treated.
- 2 I feel my muscles getting tense when the treatment actually begins.
- 3 I am frightened of the pain during and/or after the treatment.
- 4 The pain makes me nervous and restless.
- 5 I find myself worrying about the possible pain I might have to endure for every medical operation.

The % C-BSPAS for each group was obtained by calculating the total score and dividing by 5. In contrast, NOOM-treated patients

had markedly decreased C-BSPAS when compared to the controls. Indeed the % C-BSPAS in control patients was $74.6 \pm 12.8\%$ compared with $9.38 \pm 15.0\%$ in NOOM-treated patients.

Uncontrolled burns dressing pain can lead to tissue hypoxia, create biochemical and metabolic disturbances, release toxic products, and depress the cardiovascular system causing tachycardia and high blood pressure [11]. Analysis of secondary outcomes showed a significant decrease heart rate, systolic BP, diastolic BP, and a significant increase SPO_2 in NOOM-treated patients with 110 ± 23.0 versus 130 ± 27.2 , 115 ± 13.7 versus 133 ± 18.9 , 71.2 ± 10.1 versus 76.04 ± 8.94 and 99.6 ± 0.68 versus 95.8 ± 3.33 in controls ($P < 0.01$), respectively. Furthermore, a significant increase in satisfaction with current burns dressing pain management was noted in UTN compared with the UTO ($Z = -12.1$, $P < 0.01$) as well as the acceptance of NOOM from both patients and health professionals.

In this study, it was found that treatment with nitrous oxide and oxygen mixture improved primary outcomes with significantly reduction in burn dressing pain and burn pain related anxiety. The result also demonstrated great acceptance from both healthcare professionals and patients who experienced the treatment of nitrous oxide and oxygen mixture in burn dressing pain. The result proved that the model of analgesia for burn pain controlled by nitrous oxide/oxygen mixture is successful. It could potentially be implemented widely in hospital and prehospital setting and improve patients' satisfaction and quality of life in China.

Acknowledgments

The study was supported by the National Natural Science Foundation of China (70973136, 30960506 & 81160524), Ningxia Science and Technology Research Program [2012]17. We thank Dr. Margaret for editing of our manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

1. Li YX, Zhou LJ, Tang L, et al. Burn patients' experience of pain management: a qualitative study. *Burns* 2012;**38**:180–186.
2. Carrougher GJ, Ptacek JT, Honari S, et al. Self-reports of anxiety in burn-injured hospitalized adults during routine wound care. *J Burn Care Res* 2006;**27**:676–681.
3. Lai YH, Dalton JA, Belyea M. Development and testing of the pain opioid analgesics beliefs scale in Taiwanese cancer patients. *J Pain Symptom Manage* 2003;**25**:376–385.
4. Li YX, Lu T, Yu JQ, et al. Analgesia effect of a fixed nitrous oxide/oxygen mixture on burn dressing pain: study protocol. *Trials* 2012;**13**:67.
5. Montgomery RK. Pain management in burn injury. *Crit Care Nurs Clin North Am* 2004;**16**:39–49.
6. Craparo EF, Bondi ML, Pitarresi G, Cavallaro G. Nanoparticulate systems for drug delivery and targeting to the central nervous system. *CNS Neurosci Ther* 2011;**17**:670–677.
7. Rosen MA. Nitrous oxide for relief of labor pain: a systematic review. *Am J Obstet Gynecol* 2002;**186**:S110–S126.
8. Meskine N, Vullierme M, Zappa M, et al. Evaluation of analgesic effect of equimolar mixture of oxygen and nitrous oxide inhalation during percutaneous biopsy of focal liver lesions: a double-blind randomized study. *Acad Radiol* 2011;**18**:816–821.
9. Calo G, Rizzi A, Cifani C, et al. UFP-112 a potent and long-lasting agonist selective for the nociceptin/orphanin FQ receptor. *CNS Neurosci Ther* 2011;**17**:178–198.
10. Maria EE, Rosana ASD, Jayme AF, et al. Reliability and validity of the Brazilian-Portuguese version of the Burns Specific Pain Anxiety Scale. *Int J Nurs Stud* 2011;**48**:47–55.
11. Spanholtz TA, Theodorou P, Amini P, Spilker G. Severe burn injuries: acute and long-term treatment. *Dtsch Arztebl Int* 2009;**106**:607–613.