# Cold Pain Threshold and Role of NMDA Receptor Antagonists

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**Abstract-** Clonidine, the $\alpha_2$-adrenergic agonist, is usually used as an antihypertensive drug. Dextromethorphan is a non-competitive NMDA antagonist which is routinely prescribed to suppress cough. However, there are not confidential documents regarding their analgesic effects. Due to the controversies over the analgesic properties of these two drugs, this study was designed to evaluate cold pain threshold changes following their administration. This study was conducted to assess the impact of oral clonidine and dextromethorphan on ice-water immersion tolerance. Four closed sachets labeled with codes were dedicated to each participant. Each of these four sachets contained placebo, 0.3 mg/kg dextromethorphan, 0.2 mg clonidine or both of the previous drugs randomly. The cold pain threshold was measured five times for each participant, once before taking any drug (T1) and the next four times (T2-T5) after taking each of the four sachets. 35 volunteers (15 men and 20 women) participated in the study. The study showed that cold pain threshold was higher in men than women (*P*=0.004) and also in participants above 30 than those under 30-year-old (*P*=0.007). Moreover, the pain threshold did not change significantly after the administration of clonidine (*P*=0.33) or dextromethorphan (*P*=0.21), but the threshold significantly increased after receiving a combination of dextromethorphan and clonidine compared with placebo overall (*P*=0.001). Cold pain threshold was higher in men and individuals over than 30-year-old and decreased significantly after administration of clonidine and dextromethorphan conjointly. Body mass index has no relation with changes in cold pain threshold by taking mentioned medications.



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**Keywords:** Dextromethorphan; Clonidine; Cold pain threshold

## Introduction

Pain is simply described as an unpleasant feeling and has physiologic, emotional, and behavioral components. It results from biochemical reactions in three major organs: peripheral nerves, spinal cord, and brain (1). Prolonged hospitalization, decreased patients' satisfaction, and higher costs for health systems are some sequels of poorly controlled pain (1-3). Thus, interventions or medications aimed to better pain control are of great interest for researchers in recent decades.

While heat receptors are 3 to 10 times less concentrated than cold receptors, there are about 15-25 cold receptors per $cm^2$ in different parts of the human body. Depending on the temperature, a variety of responses might be elicited. For instance, only pain fibers are stimulated in very cold temperatures close to the freezing point. While 10-15° C above that temperature, pain impulses are faded and cold receptors are stimulated (Figure 1) (4). Thus, heat or cold can sometimes produce similar perception.

Cold can decrease the pain threshold through its effect on the sympathetic system activity and can increase the intensity of pain perception (5-7). When hands are immersed in icy cold water, it causes pain, and there is a direct association between the water temperature and the pain intensity. For example, the frequency of pain signals is 6 per minute at 5° C (4). Changes in the temperature of receptors are one of the factors causing changes in the receptor membrane potential and permeability, allowing the ions to move across the membrane freely and change the membrane potential. In addition, the cold results in physiologic changes like vascular contraction, congestion, and cellular inflammation (8-10).

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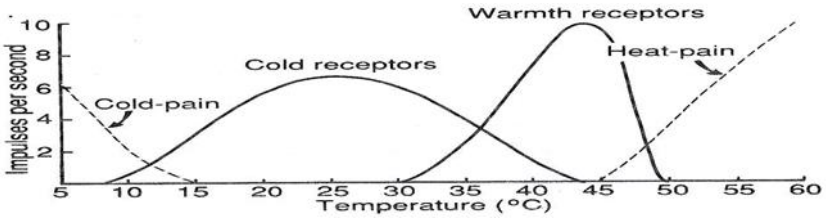


**Figure 1.** Effect of different temperatures on 4 types of receptors in the body

Using α2-agonists like clonidine and NMDA (N-Methyl-D-Aspartate) receptor antagonists like ketamine and dextromethorphan are available methods to modify pain threshold and increase the analgesic response to opioids (11).

Evidence suggests that $\alpha_2$ agonists cause analgesia in many species (12). Clonidine has been used for the management of labor pain, migraine headache, acute postoperative pain, and chronic cancer pain (13-15).

Analgesic properties of dextromethorphan as an adjuvant have been the focus of many studies in recent years (22,27,29).

NMDA receptor antagonists can prevent excessive excitability of the spinal cord. In addition, non-competitive NMDA receptor antagonists like dextromethorphan have anxiolytic, analgesic (16), and anticonvulsive properties (17-20). Moreover, some studies have shown that dextromethorphan increases the pain threshold through its effects on opioids receptors and dopaminergic pathways (11).

The authors decided to conduct this study to resolve the ambiguities and discrepancies of previous studies regarding the effective analgesic dose of the aforementioned drugs, especially when administered orally, and to clear the effect of demographic characteristics like age, sex, and BMI on pain threshold, and also to measure changes of cold pain threshold using a quantitative scale.

## Materials and Methods

This non-randomized double-blind clinical trial was conducted on 35 volunteer students and staff in a teaching hospital between May 2016 and June 2016 after obtaining approval from the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.REC.1394.2127). This study was also registered in the Iranian Registry of Clinical Trials (IRCT2016020826447N1).

All included volunteers were 18-45 years old ASA class I or II individuals. History of smoking, addiction, frequent coffee drinking, acute or chronic pain, any psychological disorder or taking any psychotropic medications was of exclusion criteria.

After getting informed consent, their demographic characteristics including age, sex, and Body Mass Index (BMI) was recorded.

We used Ice cold water (0° C) for pain induction because of its safety and steady intensity. Pain threshold was measured in 5 separate stages. The participants were requested to be present in the experiment room 30 minutes before the test. Immersing hand test was repeated 5 times for each volunteer as follows; first time before taking any drug, and the next 4 times after taking one of four packages that was encoded by researcher (each of them contained clonidine 0.2 mg or dextromethorphan equivalent to 0.3 mg/kg, clonidine plus dextromethorphan with mentioned doses and the last was placebo). The participants were first requested to immerse their hands in ice cold water (0-2° C) and inform the researcher when they felt pain or discomfort. In this stage, the duration from hand immersion in cold water to feel pain (in seconds) served as basis for the comparison of pain threshold in the later stages. We needed 0.2 mg clonidine, 0.3 mg/kg dextromethorphan, 0.2 mg clonidine+0.3 mg/kg dextromethorphan, and placebo for the next stages. The drugs were coded in medicine packets number 1 to 4 by the senior researcher and the time required by the drug to reach its peak activity was written on the corresponding packet. In the next step which was conducted on the following day, packet number 1 was selected. The participants took the drug in packet 1, and after the drug reached its peak activity, they immersed their hands in ice cold water and informed the researcher when they felt any pain or discomfort. To avoid drug interaction and their synergistic effect, a wash-out period of 10 days was considered before the next packet was used. In general, one packet was selected and used every 10 days, and the pain threshold of all participants was recorded after using all 4 packets. The data were analyzed with SPSS version 22. Frequency and mean±Standard Deviation (SD) is used to show qualitative and quantitative data, respectively. Parametric tests were used if the data had a normal distribution and non-parametric statistics were employed in the data were

not normally distributed. *P* less than 0.05 were considered significant.

## Results

Thirthy five volunteer took part in our study which is illustrated in table 1. Duration of cold pain threshold according to demographic characteristics following drug administration (in minutes) was depicted in table 2. The cold pain threshold was significantly higher in men than women in all steps (*P*=0.004). By taking either clonidine or dextromethorphan, the cold pain threshold was significantly increased, but the reduction of cold pain threshold was seen by taking clonidine+dextromethorphan that was more than women simultaneously .

Moreover, the baseline cold pain threshold was significantly higher in individuals above the age of 30 years compared with their younger counterparts (*P*=0.007) and this threshold was decreased by taking the medications alone or in combination.

Overweight and obese participants showed no significant difference in cold pain threshold compared with underweight and normal participants (*P*=0.97).

By taking dextromethorphan and clonidine+dextromethorphan, cold pain threshold increased but this change was not statistically significant (*P*>0.05).

The change in cold pain threshold was not significant after receiving 0.2 mg oral clonidine (*P*=0.33), 0.3 mg/kg oral dextromethorphan (*P*=0.23), and placebo (*P*=0.5) compared with the baseline threshold. But it was significantly higher after receiving clonidine and dextromethorphan simultaneously compared with its baseline (*P*<0.001).

Moreover, the change in cold pain threshold after receiving dextromethorphan was not significant compared with the baseline cold pain threshold (P:0.21) and cold pain threshold after receiving clonidine+dextromethorphan (*P*=0.09); however, was statistically significant when compared with the cold pain threshold after receiving placebo (*P*<0.001).

The change in cold pain threshold after receiving clonidine+dextromethorphan was statistically significant as compared with the baseline cold pain threshold (*P*=0.001) and cold pain threshold after receiving placebo (*P*=0.002).

## Discussion

Intravenous dextromethorphan (5 mg/kg) suppresses second pain response compared with oral administration (0.6 mg/kg) as Duedahla *et al*., and Hughes reported (21,22).

Analgesic properties of oral dextromethorphan have been shown in some studies, but the effective dose is not clear yet. Single doses between 30-240 mg (23), and even doses more than 300 mg have been reported to be effective for analgesia (24).

In 1997, Nelson Park reported that a dose of 400 mg/day dextromethorphan was the only effective dose for decreasing neuropathic pains (25), while Duedahl stated that dextromethorphan at a dose of 270 mg effectively suppressed neuropathic pains (21). Kauppila found that dextromethorphan at a dose of 200 mg produced severe side effects in all participants yet did not have a marked effect on mechanical pain threshold (26). Regarding effective analgesic doses of dextromethorphan, analgesia has been reported following the administration of 120 mg (27), and 45 mg/kg (28) of this drug. A study in 2014 by Reza Entezari Saeed showed that a dose of 1 mg/kg could cause analgesia (29). Most of the conducted studies have emphasized that the higher the dose of oral dextromethorphan, the greater its analgesic effects. However, the frequency of side effects like nausea and vomiting increases at higher doses (26,30).

In our study, the participants held their hands in ice cold water longer after receiving dextromethorphan compared with placebo or baseline (no drug administration), while Weinbroum *et al*., showed that different doses of dextromethorphan has no effects on the onset of pain following lower limb surgery (30).

Different studies have evaluated the analgesic effects of systemic or intrathecal clonidine alone, or in combination with other drugs like N2O, local anesthetics, or opioids , or on laboratory animals (12,13,31,32,33). Therefore, there is little data about its analgesic effects of oral administered clonidine alone and its effective analgesic dose in humans (33).

Intravenous administration of clonidine produces better analgesia as compared with its intrathecal administration but also results in more side effects. More aggressive methods of clonidine administration cause more severe side effects like hypotension or bradycardia for which vasopressors and fluid therapy can be applied (12,13,33).

In 1998, Eisenach showed that intrathecal, but not intravenous, clonidine at a dose of 150 μg reduces thermal induced hyperalgesia (34). Moreover, low doses of clonidine, for example, 2 μg/kg, in combination with bolus clonidine at a dose of 0.2 μg/kg/h or opioids have analgesic effects (32,35). IV clonidine at a dose of 75 μg

has reported being effective in postanesthetic shivering (36), but the effect of its equivalent oral dose has not been evaluated.

It was previously mentioned that oral clonidine, in addition to fewer side effects as compared with IV or intrathecal clonidine, has good oral absorption.

The physicians have shown an interest in using dextromethorphan as an adjuvant in combination with analgesics or as a drug with minimum side effects for pain management or as an efficient element in multimodal analgesia regimens. As a result, many studies have been conducted to determine the effective analgesic dose of dextromethorphan. However, it should be noted that single-dose dextromethorphan administration may not provide long-term analgesic effects due to its rather short half-life. One possible way to overcome this problem is to use multiple doses; however, more human studies are required in this regard.

In conclusion, considering the results of our study and other investigations, the effective dose of oral clonidine alone for pain suppression and pain threshold modification, especially cold pain threshold which was the focus of our study, is not clear. It seems that higher doses, with regards to their side effects, may be used for the prevention and treatment of pain. As Clonidine raises the cold threshold, thus it could be used to counteract hypothermia during the operation. Moreover, it could also be used to reduce morbidity induced by postoperative shivering. Moreover, its sedative effects and control of sympathetic responses can add to its overall useful effects for the patients.

**Table 1. Demographic characteristics of the participants**

| Table 1 | | Number (percentage) | Mean | SD |
|---|---|---|---|---|
| **Sex** | **Male** | 15 (42.9%) | -- | -- |
| | **Female** | 20 (57.1%) | -- | -- |
| **Age(year)** | | -- | 29.77 | 7.99 |
| **BMI(kg/m2 )** | | -- | 23.37 | 3 |

**Table 2. Duration of cold pain threshold according to demographic characteristics following drug administration (in minutes)**

| | | Basic time | Clonidine | Dextromethorphan | CL+DM | Placebo | *P* |
|---|---|---|---|---|---|---|---|
| **ALL** | | 2.16 (0.75-4.28) | 1.48 (0.66-5.3) | 2.58 (1.1-5.04) | 2.45 (1.37-5.33) | 1.45 (0.96-4) | <0.0001 |
| **Sex** | **Male** | 4.28 (2.2-8.41) | 5.1 (2.03-6.2) | 4.38 (2.58-8.2) | 4.04 (2.33-6.82) | 3.12 (1.45-6.28) | 0.004 |
| | **Female** | 0.86 (0.55-2.18) | 0.91 (0.6-1.91) | 1.19 (1.03-3.25) | 2.04 (1.04-2.77) | 1.1 (0.8-2.16) | |
| **Age** | **<30** | 1.04 (0.55-2.2) | 1.13 (0.61-2.13) | 1.24 (1.05-3.25) | 2.07 (1.14-3.41) | 1.1 (0.81-2.05) | 0.007 |
| | **>30** | 6.23 (2.92-9.21 ) | 5.3 (2.12-7) | 5.04 (2.9-11) | 5.02 (2.46-7.46) | 4 (2.1-7.5) | |
| **BMI** | **<25** | 2 (0.58-3.11) | 1.39 (0.64-4.8) | 2.2 (1.09-4.09) | 2.19 (1.34-4.28) | 1.28 (0.82-3.24) | 0.97 |
| | **>25** | 3.6 (1.2--7.72) | 2.21 (0.96-6.12) | 4.3 (1.95-6.55) | 3.67 (1.87-6.23) | 2.63 (1.28-5.32) | |

## References


1. Miller RD. Miller's anesthesia2015.p1901
2. Deborah B. McGuire, Connie Henke Yarbro, Ferrell B. Cancer Pain Management: Jones & Bartlett Learning; 1995.
3. Gintzler AR. Endorphin-mediated increases in pain threshold during pregnancy. Science. 1980;210(4466):193-195.
4. John E.Hall. Guyton and Hall Textbook of Medical Physiology.13th edition.2016; p630,631
5. McMurray GA, Jaques LB. Capillary resistance and blood pressure changes associated with pain due to local cooling: cold pressor test. Journal of Applied Physiology. 1959;14(5):813-816.
6. Simone DA, Kajander KC. Responses of cutaneous A-fiber nociceptors to noxious cold. J Neurophysiol. 1997;77(4):2049-2060.
7. Wolf S, Hardy JD. Studies on Pain. Observations on Pain Due to Local Cooling and on Factors Involved in the "Cold Pressor" Effect. J Clin Invest. 1941;20(5):521-533.
8. Hines EA, Jr, Brown GE. A standard test for measuring the

variability of blood pressure: Its significance as an index of the prehypertensive state*. Annals of Internal Medicine. 1933;7(2):209-217.

9. Kreh A, Anton F, Gilly H, Handwerker HO. Vascular reactions correlated with pain due to cold. Experimental Neurology. 1984;85(3):533-546.
10. Lovallo W. The cold pressor test and autonomic function: a review and integration. Psychophysiology. 1975;12(3):268-282.
11. Farzin D, Mehrabian M. Ëvaluation of opioid and dopaminergic mechanisms of dextromethorphan on the nociceptive response-induced by hot plate in mice. Journal of Mazandaran University of Medical Sciences. 2004;14(45):1-15.
12. Hao JX, Yu W, Xu XJ, Wiesenfeld-Hallin Z. Effects of intrathecal vs. systemic clonidine in treating chronic allodynia-like response in spinally injured rats. Brain Res. 1996;736(1-2):28-34.
13. Siiba S, Nakanishi O, Ishikawa T, Hirakawa T, Kawahara H, Imamura Y. Increase in the threshold of pain and touch sensation in the human face with clonidine plus 30% nitrous oxide. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87(3):294-298.
14. Walker SM, Grafe M, Yaksh TL. Intrathecal clonidine in the neonatal rat: dose-dependent analgesia and evaluation of spinal apoptosis and toxicity. Anesth Analg. 2012;115(2):450-460.
15. Kumar A, Maitra S, Khanna P, Baidya DK. Clonidine for management of chronic pain: A brief review of the current evidences. Saudi J Anaesth. 2014;8(1):92-96.
16. Ilkjaer S, Bach LF, Nielsen PA, Wernberg M, Dahl JB. Effect of preoperative oral dextromethorphan on immediate and late postoperative pain and hyperalgesia after total abdominal hysterectomy. Pain. 2000;86(1-2):19-24.
17. Church J, Jones MG, Davies SN, Lodge D. Antitussive agents as N-methylaspartate antagonists: further studies. Canadian Journal of Physiology and Pharmacology. 1989/06/01 1989;67(6):561-567.
18. Wong BY, Coulter DA, Choi DW, Prince DA. Dextrorphan and dextromethorphan, common antitussives, are antiepileptic and antagonize N-methyl-D-aspartate in brain slices. Neurosci Lett. 1988;85(2):261-266.
19. Elliott KJ, Brodsky M, Hynansky A, Foley KM, Inturrisi CE. Dextromethorphan shows efficacy in experimental pain (nociception) and opioid tolerance. Neurology. December 1, 1995 1995;45(12 Suppl 8):S66-S68.
20. Elliott KJ, Brodsky M, Hynansky AD, Foley KM, Inturrisi CE. Dextromethorphan suppresses both formalin-induced nociceptive behavior and the formalin-induced increase in spinal cord c-fos mRNA. Pain. 1995;61(3):401-409.
21. Duedahl TH, Dirks J, Petersen KB, Romsing J, Larsen NE, Dahl JB. Intravenous dextromethorphan to human volunteers: relationship between pharmacokinetics and anti-hyperalgesic effect. Pain. 2005;113(3):360-368.
22. Hughes AM, Rhodes J, Fisher G, Sellers M, Growcott JW. Assessment of the effect of dextromethorphan and ketamine on the acute nociceptive threshold and wind-up of the second pain response in healthy male volunteers. Br J Clin Pharmacol. 2002;53(6):604-612.
23. Duedahl TH, Romsing J, Moiniche S, . DJ. A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. Acta Anaesthesiol Scand. 2006;50:1-13.
24. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. Pain. 1999;83(3):389-400.
25. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology. 1997;48(5):1212-1218.
26. Kauppila T, Gronroos M, Pertovaara A. An attempt to attenuate experimental pain in humans by dextromethorphan, an NMDA receptor antagonist. Pharmacol Biochem Behav. 1995;52(3):641-644.
27. Ilkjaer S, Dirks J, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. Br J Anaesth. 1997;79(5):600-605.
28. McConaghy PM, McSorley P, McCaughey W, Campbell WI. Dextromethorphan and pain after total abdominal hysterectomy. Br J Anaesth. 1998;81(5):731-736.
29. Entezary SR, Farshadpour S, Alebouyeh MR, Imani F, Emami Meybodi MK, Yaribeygi H. Effects of preoperative use of oral dextromethorphan on postoperative need for analgesics in patients with knee arthroscopy. Anesth Pain Med. 2013;4(1.(
30. Weinbroum AA, Lalayev G, Yashar T, Ben-Abraham R, Niv D, Flaishon R. Combined pre-incisional oral dextromethorphan and epidural lidocaine for postoperative pain reduction and morphine sparing: a randomised double-blind study on day-surgery patients. Anaesthesia. 2001;56(7):616-622.
31. De Negri P, Ivani G, Visconti C, De Vivo P, Lonnqvist PA. The dose-response relationship for clonidine added to a postoperative continuous epidural infusion of ropivacaine in children. Anesth Analg. 2001;93(1):71-76.
32. Stocche RM, Garcia LV, Klamt JG, dos Reis MP, Gil DR, Mesquita KL. Influence of intravenous clonidine in the cost of sevoflurane anesthesia for outpatient middle ear procedures. Rev Bras Anestesiol. 2004;54(1):91-98.

33. Carroll D, Jadad A, King V, Wiffen P, Glynn C, McQuay H. Single-dose, randomized, double-blind, double-dummy cross-over comparison of extradural and i.v. clonidine in chronic pain. Br J Anaesth. 1993;71(5):665-669.
34. Eisenach JC, Hood DD, Curry R. Intrathecal, but not intravenous, clonidine reduces experimental thermal or capsaicin-induced pain and hyperalgesia in normal volunteers. Anesth Analg. 1998;87(3):591-596.
35. Bernard MDJ-M, Hommeril MDJ-L, Passutl MDPDN, Pinaud MDPDM. Postoperative Analgesia by Intravenous Clonidine. Anesthesiology. 1991;75(4):577-582.
36. Compton P, Charuvastra VC, Ling W. Effect of oral ketorolac and gender on human cold pressor pain tolerance. Clin Exp Pharmacol Physiol. 2003;30(10):759-763.