Anesth Pain Med. 2017 June; 7(3):e45297. doi: 10.5812/aapm.45297.

Published online 2017 April 26. **Research Article**

A Comparative Study on the Efficacy of Oral Memantine and Placebo for Acute Postoperative Pain in Patients Undergoing Dacryocystorhinostomy (DCR)

Poupak Rahimzadeh,[1] Farnad Imani,[1] Nasim Nikoubakht,[1] Zahra Koleini,[1] Seyed Hamid Reza Faiz,[1,*] and Azadeh Sayarifard[2]

[1]Pain Research Center, Department of Anesthesiology and Pain Medicine, Rasoul-Akram Medical Center, Iran University of Medical Sciences, Tehran, Iran
[2]Center for Academic and Health Policy, Tehran University of Medical Sciences, Tehran, Iran

[*]*Corresponding author*: Seyed Hamid Reza Faiz, Pain Research Center, Department of Anesthesiology and Pain Medicine, Rasoul-Akram Medical Center, Iran University of Medical Sciences, Tehran, Iran. Tel: +98-9121534811, Fax: +98-2166509059, E-mail: hrfaiz@hotmail.com

Received 2017 January 18; **Revised** 2017 March 15; **Accepted** 2017 April 08.

Abstract

Background: Memantine is an N-methyl-D-Aspartate (NMDA) antagonist. By transferring acute postoperative pain, the NMDA channels may lead to active excess and neuropathic pain. Objectives: This study attempted to investigate the effect of preoperative use of single oral dose of memantine in controlling Dacryocystorhinostomy (DCR) postoperative pain.
Methods: A double-blind clinical trial was conducted on 60 patients undergoing DCR. On arrival at the operating room, the memantine group received 20 mg of oral memantine and the control group received placebo. The severities of pain by visual analogue scale (VAS) and sedation by Ramsy Scale were measured immediately 1, 2, and 6 hours after the operation. The drug's side effects were recorded.
Results: The pain scores of patients in the recovery in 1, 2, and 6 hours after operation were significantly lower in the memantine group than the placebo group ($P < 0.001$). The sedation score, 1 hour after the operation, was significantly greater in the memantine group than the placebo ($P < 0.001$). The sedation scores did not have any statistically significant difference in recovery and 2 hours after surgery between the two groups. Moreover, the sedation scores in 6 hours after the surgery were identical in the two groups.
Conclusions: The oral single-dose 20 mg of memantine administered before DCR can reduce postoperative pain compared with placebo.

Keywords: Dacryocystorhinostomy, Pain, Postoperative, Memantine, Placebo

1. Background

Dacryocystorhinostomy is one of the most common oculoplastics surgeries (1). DCR causes mild to moderate postoperative pain (2). The postoperative pain control practices pose one of the major challenges in anesthesia and surgery (3, 4). Various methods have been proposed for that purpose and acute pain services are provided in hospitals, even though the techniques to curtail postoperative acute pain, ranging from the prescription of painkillers before operation to central and peripheral nerve blocks, each have proven their own especially useful effects (5-8).

Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are administered to control the pain after eye surgeries; because of the known side effects of these drugs, administering other drugs to reduce patient's pain can be useful in dealing with the postoperative pain (2).

The N-methyl-D-Aspartate (NMDA) receptors play an important role in the sensitization of both central peripheral sensory systems. Hence, pain can be caused when antagonists block NMDAs (9, 10).

Memantine is an oral example of NMDA antagonists. The main function of memantine is the blockage of the current flow through NMDA channel receptor (11-13). This drug has a moderate affinity to NMDA-NR2B receptor. It also affects the nicotinic and 5-HT3 receptors (14).

Some studies have shown that memantine is able to prevent postoperative pain if administered prior to nerve injuries. However, it is crucial to carry out further RCT studies in homogeneous groups of patients to explore the therapeutic potential of memantine for relieving postoperative pain (9, 15, 16).

2. Objectives

This study attempted to investigate the effect of preoperative use of single oral dose of memantine in controlling DCR postoperative pain.

3. Methods

This was a double blind randomized clinical trial. The study was approved by the Ethics Committee at Iran University of Medical Sciences and then registered at IRCT. Samples were selected among the patients referring to Rasoul Akran Hospital in Iran University of Medical Sciences in Tehran during 2013 - 2014.

The sample size was calculated to be 60 based on alpha error of 0.05 and power of 80%. Inclusion criteria were patients aged 20 to 70 years, ASA class II-I candidates for DCR, able to communicate verbally or in writing and who consented to participate in the study.

The exclusion criteria were cardiovascular and respiratory diseases, dizziness and frequent headaches, drug abuse and alcohol consumption, daily analgesia or 48 hours before operation, renal failure, impaired hepatic function, and patient refusal.

In this double-blind study, the patients and the anesthesiologist who assessed the pain and medical complications were completely unaware of the type of drugs administered.

Based on a computer-derived randomization list, the patients were randomly divided into two groups of 30. The groups were called memantine group and the control group. Immediately upon arrival at the operating room, the memantine group received 20 mg of oral memantine (Daroupakhsh, Iran, tab 10 mg) and control group received placebo.

Midazolam 0.3 mg/kg, fentanyl 2 mcg/kg, and then cis atracurium besylate 0.2 mg/kg and thiopental 5 mg/kg were administered for both groups. The patients were intubated and underwent surgery through 100 mcg/kg/min of propofol for the maintenance of anesthesia.

The intensity of pain (0 = no pain, 10 = worse possible pain) was measured through visual analogue scale (VAS) at recovery in 1, 2, and 6 hours after operation.

The sedation severity was specified by an anesthesiologist at the same intervals. The Ramasy criteria was used for this variable.

Ramsay Sedation Assessment scale: 1- patient anxious or agitated or both; 2- patient cooperative, oriented, and tranquil; 3- patient response to commands only; 4- a brisk response to a light glabellar tap; 5- a sluggish response to a light glabellar tap; 6- no response

Incidence of nausea and vomiting were evaluated during the study. The demographic data, pain, and drug side effects were obtained and recorded in already prepared forms.

In order to make the study double blind, the patients and the researcher were not aware of the type of intervention done in the memantine and control groups.

The data were imported into SPSS 18. Frequencies and percentages were calculated for qualitative variable, while means and standard deviations were reported for quantitative variables. The normal distribution of data was examined through the Kolmogorov-Smirnov test. Data were analyzed through Chi-square, T-test, or non-parametric tests as required. In the statistical analysis, P value < 0.05 was considered significant.

4. Results

The demographic information of patients has been displayed separately in Table 1, where there was no statistically significant difference. Duration of surgery was between 2 to 3 hours.

Pain scale in recovery in 1, 2, and 6 hours after operation was significantly lower in the memantine group than the placebo group (Table 1).

Sedation scale one hour after the operation was significantly greater in the memantine group than the placebo ($P < 0.001$). Moreover, the sedation scores in 6 hours after the surgery were identical in the two groups (Table 1).

Nausea - vomiting occurred in the memantine group in 6 subjects (20%) the placebo group in 7 subjects (23%), indicating no significant difference ($P = 0.7$).

5. Discussion

The NMDA receptor antagonists such as memantine are expected to be effective in reducing postoperative pain (14). Memantine is safe and well-tolerated in patients (17). Memantine is absorbed from the gastrointestinal tract with plasma concentration peaking within 3 to 7 hours. Plasma elimination half-life of memantine is 60 to 80 hours, and a majority of memantine is excreted unchanged in urine (18).

The current study showed that 20 mg of memantine reduced postoperative pain in patients undergoing DCR. The pain scores of patients in recovery in 1, 2, and 6 hours after the operation were significantly lower in the memantine group than the placebo group.

Moreover, consciousness after the operation impaired the anesthetic assessments. More sleepy patients after operation may face complications such as vomiting after feeding, aspiration of vomited substances, and eventually pneumonia. Drowsiness after operation also requires greater patient care accompanied by higher risks of falling and other hazards. This study demonstrated the sedation scale 1 hour after the operation in the memantine group was significantly greater than placebo. Hence, memantine can be administered to patients whose condition and type of operation allow early discharge.

Table 1. Demographic Data, Visual Analog Scale and Sedation Scale in Terms of Two Groups[a]

Variable		Placebo (n = 30)	Memantine (n = 30)	P Value
Age, y		43.8 ± 10.5	46.3 ± 10.7	0.3
Gender (female/male)		18/12	18/12	1
BMI, kg/m^2		23.9 ± 3.0	24.9 ± 3.4	0.2
Visual Analog Scale	Recovery	4.7 ± 0.8	3.3 ± 0.7	< 0.001
	1 hour after operation	3.7 ± 0.8	2.3 ± 0.7	< 0.001
	2 hours after operation	2.8 ± 0.9	1.6 ± 1.2	< 0.001
	6 hours after operation	2.8 ± 0.9	1 .0 ± 0.9	< 0.001
Sedation scale	Recovery	1.0 ± 0.8	1.0 ± 0.7	0.3
	1 hour after operation	1.2 ± 0.6	1.7 ± 0.7	< 0.001
	2 hours after operation	1.9 ± 0.9	2.0 ± 1.2	0.3
	6 hours after operation	2.0 ± 0.0	2.0 ± 0.0	1

[a]Values are expressed as mean ± SD.

Morel et al. (15) examined the effect of memantine on the reduction of postoperative pain in mastectomy. In this study, memantine was administered at a dose of 5 to 20 mg daily after mastectomy for two weeks. The study showed that postoperative pain significantly decreased in patients who received memantine compared with the control group.

In a study on the effect of NMDA receptor of memantine on reducing acute pain at the withdrawal phase of opioids, Harris et al. (19) showed that NMDA receptors may play a key role in the early stages of drug dependence, where memantine can be useful for the treatment of addiction and acute pain.

Emik et al. (20) showed, in an animal clinical trial, memantine reduced recovery times and postoperative pain and provided better cognitive functions after propofol anesthesia.

Goebel reported the effect of memantine for the treatment of long-standing complex regional pain syndrome (21).

Several studies reported memantine is effective for controlling neuropathic pain (22-25). Some studies also showed the efficacy of memantine in the treatment of fibromyalgia (26, 27).

Some studies also obtained results inconsistent with those of our study concerning the effect of memantine on reducing pain. In a systematic review study, Collins et al. (9) suggested that there is insufficient evidence regarding the effectiveness of NMDA receptor antagonists on neuropathic pain. Nikolajsen et al. (28) demonstrated that compared with placebo, memantine at a dose of 20 mg/d did not relieve the pain in patients with nerve damage.

5.1. Conclusions

The oral single-dose 20 mg of memantine administered before DCR can reduce postoperative pain compared with placebo.

Acknowledgments

The authors wish to acknowledge the contribution of all people who helped us in this study.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ali MJ, Naik MN, Honavar SG. External dacryocystorhinostomy: Tips and tricks. *Oman J Ophthalmol.* 2012;**5**(3):191–5. doi: 10.4103/0974-620X.106106. [PubMed: 23440476].
2. Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. *Anesth Pain Med.* 2012;**2**(2):72–6. doi: 10.5812/aapm.4301. [PubMed: 24223341].
3. Imani F, Safari S. "Pain Relief is an Essential Human Right", We Should be Concerned about It. *Anesth Pain Med.* 2011;**1**(2):55–7. doi: 10.5812/kowsar.22287523.2306. [PubMed: 25729655].
4. Rahimzadeh P, Imani F, Faiz SH, Nikoubakht N, Sayarifard A. Effect of intravenous methylprednisolone on pain after intertrochanteric femoral fracture surgery. *J Clin Diagn Res.* 2014;**8**(4):GC01–4. doi: 10.7860/JCDR/2014/8232.4305. [PubMed: 24959459].
5. Imani F. Postoperative pain management. *Anesth Pain Med.* 2011;**1**(1):6–7. doi: 10.5812/kowsar.22287523.1810. [PubMed: 25729647].

6. Joshi G, Gandhi K, Shah N, Gadsden J, Corman SL. Peripheral nerve blocks in the management of postoperative pain: challenges and opportunities. *J Clin Anesth.* 2016;**35**:524–9. doi: 10.1016/j.jclinane.2016.08.041. [PubMed: 27871587].
7. Lovich-Sapola J, Smith CE, Brandt CP. Postoperative pain control. *Surg Clin North Am.* 2015;**95**(2):301–18. doi: 10.1016/j.suc.2014.10.002. [PubMed: 25814108].
8. Penprase B, Brunetto E, Dahmani E, Forthoffer JJ, Kapoor S. The efficacy of preemptive analgesia for postoperative pain control: a systematic review of the literature. *AORN J.* 2015;**101**(1):94–105 e8. doi: 10.1016/j.aorn.2014.01.030. [PubMed: 25537330].
9. Collins S, Sigtermans MJ, Dahan A, Zuurmond WW, Perez RS. NMDA receptor antagonists for the treatment of neuropathic pain. *Pain Med.* 2010;**11**(11):1726–42. doi: 10.1111/j.1526-4637.2010.00981.x. [PubMed: 21044263].
10. Wiech K, Kiefer RT, Topfner S, Preissl H, Braun C, Unertl K, et al. A placebo-controlled randomized crossover trial of the N-methyl-D-aspartic acid receptor antagonist, memantine, in patients with chronic phantom limb pain. *Anesth Analg.* 2004;**98**(2):408–13. [PubMed: 14742379] table of contents.
11. Gustin SM, Schwarz A, Birbaumer N, Sines N, Schmidt AC, Veit R, et al. NMDA-receptor antagonist and morphine decrease CRPS-pain and cerebral pain representation. *Pain.* 2010;**151**(1):69–76. doi: 10.1016/j.pain.2010.06.022. [PubMed: 20630656].
12. Lindelof K, Bendtsen L. Memantine for prophylaxis of chronic tension-type headache–a double-blind, randomized, crossover clinical trial. *Cephalalgia.* 2009;**29**(3):314–21. doi: 10.1111/j.1468-2982.2008.01720.x. [PubMed: 19220313].
13. Recla JM, Sarantopoulos CD. Combined use of pregabalin and memantine in fibromyalgia syndrome treatment: a novel analgesic and neuroprotective strategy?. *Med Hypotheses.* 2009;**73**(2):177–83. doi: 10.1016/j.mehy.2009.01.052. [PubMed: 19362430].
14. Hackworth RJ, Tokarz KA, Fowler IM, Wallace SC, Stedje-Larsen ET. Profound pain reduction after induction of memantine treatment in two patients with severe phantom limb pain. *Anesth Analg.* 2008;**107**(4):1377–9. doi: 10.1213/ane.0b013e31817f90f1. [PubMed: 18806054].
15. Morel V, Joly D, Villatte C, Dubray C, Durando X, Daulhac L, et al. Memantine before Mastectomy Prevents Post-Surgery Pain: A Randomized, Blinded Clinical Trial in Surgical Patients. *PLoS One.* 2016;**11**(4):e0152741. doi: 10.1371/journal.pone.0152741. [PubMed: 27050431].
16. Suzuki M. Role of N-methyl-D-aspartate receptor antagonists in postoperative pain management. *Curr Opin Anaesthesiol.* 2009;**22**(5):618–22. doi: 10.1097/ACO.0b013e32832e7af6. [PubMed: 19535974].
17. Kavirajan H. Memantine: a comprehensive review of safety and efficacy. *Expert Opin Drug Saf.* 2009;**8**(1):89–109. doi: 10.1517/14740330802528420. [PubMed: 19236221].
18. Ferris SH. Evaluation of memantine for the treatment of Alzheimer's disease. *Expert Opin Pharmacother.* 2003;**4**(12):2305–13. doi: 10.1517/14656566.4.12.2305. [PubMed: 14640929].
19. Harris AC, Rothwell PE, Gewirtz JC. Effects of the NMDA receptor antagonist memantine on the expression and development of acute opiate dependence as assessed by withdrawal-potentiated startle and hyperalgesia. *Psychopharmacology (Berl).* 2008;**196**(4):649–60. doi: 10.1007/s00213-007-0998-2. [PubMed: 18026718].
20. Emik U, Unal Y, Arslan M, Demirel CB. [The effects of memantine on recovery, cognitive functions, and pain after propofol anesthesia]. *Rev Bras Anestesiol.* 2016;**66**(5):485–91. doi: 10.1016/j.bjan.2015.03.002. [PubMed: 27445259].
21. Goebel A. Morphine and memantine treatment of long-standing complex regional pain syndrome. *Pain Med.* 2012;**13**(3):357–8. doi: 10.1111/j.1526-4637.2011.01317.x. [PubMed: 22295900].
22. Buvanendran A, Kroin JS. Early use of memantine for neuropathic pain. *Anesth Analg.* 2008;**107**(4):1093–4. doi: 10.1213/ane.0b013e318180ebfe. [PubMed: 18806007].
23. Grande LA, O'Donnell BR, Fitzgibbon DR, Terman GW. Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient. *Anesth Analg.* 2008;**107**(4):1380–3. doi: 10.1213/ane.0b013e3181733ddd. [PubMed: 18806055].
24. Pickering G, Morel V, Joly D, Villatte C, Roux D, Dubray C, et al. Prevention of post-mastectomy neuropathic pain with memantine: study protocol for a randomized controlled trial. *Trials.* 2014;**15**:331. doi: 10.1186/1745-6215-15-331. [PubMed: 25142039].
25. Rogers M, Rasheed A, Moradimehr A, Baumrucker SJ. Memantine (Namenda) for neuropathic pain. *Am J Hosp Palliat Care.* 2009;**26**(1):57–9. doi: 10.1177/1049909108330025. [PubMed: 19196860].
26. Olivan-Blazquez B, Herrera-Mercadal P, Puebla-Guedea M, Perez-Yus MC, Andres E, Fayed N, et al. Efficacy of memantine in the treatment of fibromyalgia: A double-blind, randomised, controlled trial with 6-month follow-up. *Pain.* 2014;**155**(12):2517–25. doi: 10.1016/j.pain.2014.09.004. [PubMed: 25218600].
27. Olivan-Blazquez B, Puebla M, Masluk B, Perez-Yus MC, Arcega R, Andres E, et al. Evaluation of the efficacy of memantine in the treatment of fibromyalgia: study protocol for a doubled-blind randomized controlled trial with six-month follow-up. *Trials.* 2013;**14**:3. doi: 10.1186/1745-6215-14-3. [PubMed: 23286311].
28. Nikolajsen L, Gottrup H, Kristensen AG, Jensen TS. Memantine (a N-methyl-D-aspartate receptor antagonist) in the treatment of neuropathic pain after amputation or surgery: a randomized, double-blinded, cross-over study. *Anesth Analg.* 2000;**91**(4):960–6. [PubMed: 11004057].