

## Effect of Nano-Particle of Magnesium Oxide on Ketamine-Induced Anesthesia in Rabbit

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**Abstract:** Some studies show magnesium has analgesic effect in some pain models but this evaluation was not carried on nano-Magnesium Oxide (MgO). Thus, present study was designed to evaluation effect of Mgo nano-particles and conventional MgO on ketamine-induced anesthesia in rabbits. At this study, 20 adult rabbits were used in 4 groups. Ketamine was intrapritoneally injected in all groups and xylazine, MgO nanoparticle and MgO suspension was administrated 15 min before ketamine injection in 3 last groups. The rectal temperature, respiratory rate and heart rate were measured before drug administration and during of anesthesia. Duration of anesthesia and recovery time was recorded. The mean of body temperature and heart rate changed in groups but this change was not significant except group1 which received only ketamine. The mean of respiratory rate significantly decreased before and after anesthesia in all groups but this decreasing was greater (nearly 3 fold) in group 2 which received ketemine and xylazine. Also duration of anesthesia was longer significantly in this group. Thus quality and duration of ketamine-induced anesthesia did not differ by MgO-nanoparticles with comparison to conventional MgO.

**Keywords:** Anesthesia, ketamine, mgo nano-particles, rabbit

### INTRODUCTION

Magnesium as an important ion of body have a limited level in the serum (0.3% of total body magnesium), where it is in three states-ionized (62%), protein bound (33%), and those bound mainly to albumin and complexed to anions (Fawcett *et al.*, 1999). Its half-life varying between 41 and 181 days and equilibrium between tissue pools is reached slowly (Wolf and Cittadini, 2003).

Magnesium as a noncompetitive blocker of N-Methyl D-Aspartate (NMDA) receptor inhibits calcium entry into the cell (Mayer *et al.*, 1984). Begon *et al.* (2001) and Hasanein *et al.* (2007) indicated that the magnesium and NMDA receptor involve in the modulation of pain. The NMDA receptor antagonism inhibits induction and maintenance of central sensitization after nociceptive stimuli. Magnesium is also a physiological calcium antagonist at different voltage-gated channels, which may be important in the mechanisms of anti nociception (Fawcett *et al.*, 1999). Bolcal *et al.* (2005) showed that magnesium potentiates analgesic effect of opioids.

Ketamine is a NMDA receptor blocker and used as injectable anesthetic agent. Xylazine is a  $\alpha_2$ -adrenoceptor-agonist which acts on the pre-and postsynaptic nerve terminals. The combination of ketamine and xylazine has been used for many species

over the years and remains a popular combination for intramuscular and intravenous anesthesia in animals including rabbits (Difilippo *et al.*, 2004; Baumgartner *et al.*, 2010).

Conventional drugs suffer from the major limitation of adverse effects, the result of the non-specificity of their action and from a lesser effectiveness due to improper or ineffective dosages, e.g., in cancer chemotherapy and anti-diabetic therapy (Chekman, 2008). Nanotechnology offers the possibility of designing new drugs with greater cell specificity and drug-release systems that act selectively on specific targets. This allows the administration of smaller but more effective doses, minimizing adverse effects. Nanotechnology can also be used to optimize drug formulations, increasing drug solubility and altering the pharmacokinetics to sustain the release of the drug, thereby prolonging its bioavailability (Ghrab *et al.*, 2009; Kaya *et al.*, 2009).

Since the effect of nano-MgO did not evaluate for anesthesia; aim of present study was evaluation and comparison its effect with conventional MgO in ketamine-induced anesthesia.

### MATERIALS AND METHODS

This experimental study was conducted in Iran-Ahvaz-Shahid Chamran University in spring of 2012.

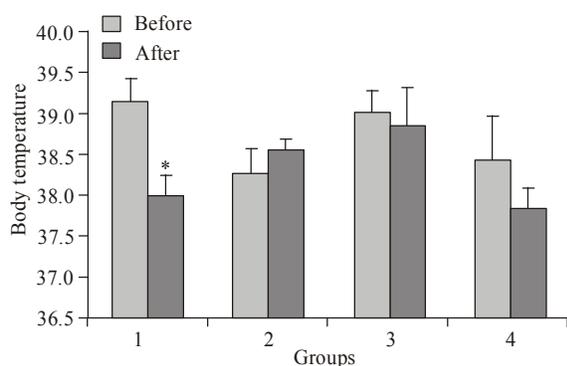


Fig. 1: Mean±SEM of rectal temperature (C°) before and after anesthesia in rabbits (n = 5 each group)  
 1: ketamine; 2: ketamine+xylazine; 3: ketamine+nano-Mg O; 4: ketamine+conventional MgO; \*: Significant difference (p<0.05)

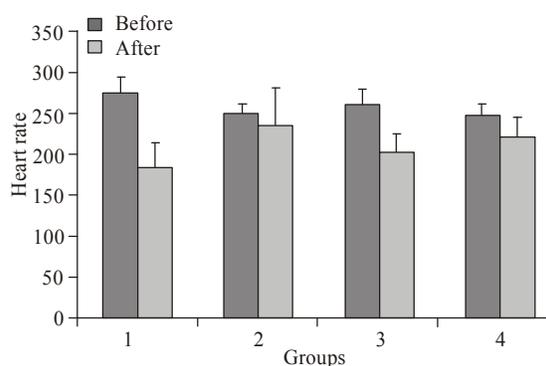


Fig. 2: Mean±SEM of heart rate (per min) before and after anesthesia in rabbits (n = 5 each group)  
 1: ketamine; 2: ketamine+xylazine; 3: ketamine+nano-MgO; 4: ketamine+conventional MgO; \*: Significant difference (p<0.05)

At present study, we used 20 adult mixed breed rabbits (1.1 to 1.7 kg) in 4 groups. Rectal temperature, respiratory rate and heart rate were measured. Drugs were administrated as following:

- **Group 1:** Only ketamine (40 mg/kg intramuscularly) (Elsa *et al.*, 2005)
- **Group 2:** Xylazine (5 mg/kg intramuscularly) and 15 min later ketamine (40 mg/kg intramuscularly)
- **Group 3:** MgO-nanoparticles suspension (5 mg/kg intraperitoneally) and 15 min later ketamine (40 mg/kg intramuscularly)
- **Group 4:** MgO suspension (5 mg/kg intraperitoneally) and 15 min later ketamine (40 mg/kg intramuscularly)

After induction of anesthesia and at surgical stage, the rectal temperature, respiratory rate and heart rate were measured again. Duration of anesthesia and time of recovery was recorded.

Statistical significance between groups was determined using SPSS program (USA, version16). The minimum level of significance was p<0.05.

## RESULTS

The mean of body temperature changed in groups but this change was not significant except group1 which received only ketamine (Fig. 1). The mean of body temperature significantly decreased in this group (p = 0.005). There were no differences in heart rate before and after anesthesia in all groups except group 1 (Fig. 2). The mean of heart rate significantly decreased in this group (p = 0.002).

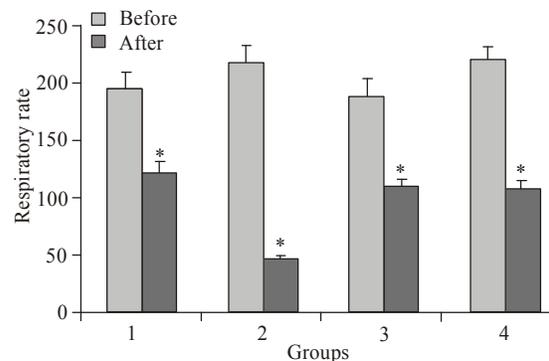


Fig. 3: Mean±SEM of respiratory rate (per min) before and after anesthesia in rabbits (n = 5 each group)  
 1: Ketamine; 2: ketamine+xylazine; 3: Ketamine+nano-MgO; 4: ketamine+conventional MgO; \*: Significant difference (p<0.05)

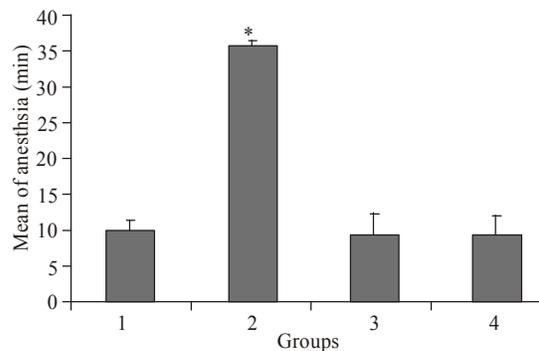


Fig. 4: Mean±SEM of duration of anesthesia in rabbits (n = 5 each group)  
 1: ketamine; 2: ketamine+xylazine; 3: ketamine+nano-MgO; 4: ketamine+conventional MgO; \*: Significant difference (p<0.05)

The mean of respiratory rate significantly decreased before and after anesthesia in all groups ( $p < 0.05$ ) (Fig. 3). But this decreasing was greater (nearly 3 fold) in group 2 which received ketamine and xylazine.

Duration of anesthesia was longer significantly in group 2 which received ketamine and xylazine with comparison to other groups ( $p < 0.05$ ) (Fig. 4). Recovery time was not different between groups statistically.

## DISCUSSION

Magnesium is a bivalent ion, the fourth most common cation in the body, and the second most common intracellular cation after potassium. Historically, magnesium sulphate has been proposed as a general anesthetic. Magnesium reduces the catecholamine release. Magnesium has also antinociceptive effects in animal and human models of pain by blocking the N-methyl-D-aspartate receptor and the associated ion channels and thus preventing central sensitization caused by peripheral nociceptive stimulation. So for some authors it reduces the need for intraoperative anesthetics and relaxant drugs and reduces the amount of morphine for the treatment of postoperative pain. The use of magnesium is extended not only to general anesthesia but also in loco-regional anesthesia (Soave *et al.*, 2009). Magnesium is also a physiological calcium antagonist at different voltage-gated channels (Iseri and French, 1984) which may be important in the mechanisms of antinociception (Mantyh *et al.*, 1994). This provides further evidence that Mg<sup>2+</sup> blocks inward current flow through ion channels linked to NMDA receptors (Mayer *et al.*, 1984). It may be suggested that magnesium may be considered as one of the ingredients of multimodal analgesic stratagems in reducing the severity of post-thoracotomy pain.

Magnesium reduces catecholamine release and thus allows better control of adrenergic response during intubation or pheochromocytoma surgery. It also decreases the frequency of postoperative rhythm disorders in cardiac. The use of adjuvant magnesium during perioperative analgesia may be beneficial for its antagonist effects on N-methyl-D-aspartate receptors (Dubé and Granry, 2003). Magnesium sulphate has anesthetic, analgesic and muscle relaxation effects and significantly reduces the drug requirements of propofol, rocuronium and fentanyl during anesthesia (Gupta *et al.*, 2006). Also magnesium deficiency induces a sensitization of nociceptive pathways in the spinal cord (Begon *et al.*, 2001). Ionized magnesium concentration decreases during surgery under general anesthesia, in part, possibly by the effect of anesthetic agent on the cell membrane itself (Okuda *et al.*, 1999).

Ketamine and magnesium block NMDA receptors and might therefore be useful analgesics, and combinations of magnesium and ketamine provide more effective analgesia (Liu *et al.*, 2001). The duration of analgesia with the lumbosacral epidural ketamine-magnesium combination was more than twice that obtained with them alone (Derossi *et al.*, 2012).

Gupta *et al.* (2011) demonstrated magnesium sulfate significantly increased the mean and maximum duration of analgesia in thoracic epidural block. The MgO nano-particles did not have more effect than conventional MgO in our study. But we think the nano-particles may greater penetrate to site action of ketamine and more potentiate its effect.

## CONCLUSION

It seems that the quality and duration of ketamine-induced anesthesia did not differ by MgO-nanoparticles with comparison to conventional Mg-O by dosage which applied at present study.

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