Vein pretreatment with magnesium sulfate to prevent pain on injection of propofol is not justified

[Un prétraitement veineux au sulfate de magnésium n'est pas justifié pour prévenir la douleur causée par l'injection de propofol]

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Purpose: Propofol produces anesthesia with rapid recovery. However, it causes pain or discomfort on injection. A number of techniques have been tried for minimizing propofol-induced pain with variable results. We have compared the efficacy of magnesium and lidocaine for the prevention of propofol induced pain.

Methods: Three hundred ASA I and II adults undergoing elective surgery were randomly assigned into three groups of 100 each. Group I received magnesium sulfate 1 g, Group II received lidocaine 2% (40 mg) and Group III received normal saline, all in a volume of 2 mL and accompanied by venous occlusion for one minute. Induction with propofol 2.5 mg·kg⁻¹ was accomplished following the release of venous occlusion. Pain was assessed on a four-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain at the time of pretreatment and propofol injection. Results were analyzed by 'Z' test. A P value of < 0.05 was considered as significant.

Results: Pain during iv pretreatment with magnesium was 31% as compared to 2% for both the lidocaine and control groups ($P < 0.05$). Seventy-six percent of patients in the control group had pain during iv propofol as compared to 32% and 42% in the magnesium and the lidocaine groups respectively ($P < 0.05$). Lidocaine and magnesium pretreatment were equally effective in attenuating pain during the propofol injection ($P > 0.05$).

Conclusions: Intravenous magnesium and lidocaine pretreatment are equally effective in attenuating propofol-induced pain. However, magnesium pretreatment itself causes pain. Therefore, there is no justification in the use of magnesium pretreatment for attenuating pain associated with iv propofol.

Objectif: Le propofol produit une anesthésie dont la récupération est rapide. Son injection cause toutefois de la douleur ou de l'inconfort. On a tenté de réduire cette douleur au moyen de quelques techniques aux résultats variables. Nous avons comparé l'efficacité du magnésium et de la lidocaïne pour prévenir la douleur induite par le propofol.

Méthode : Trois cents adultes d'état physique ASA I et II devant subir une intervention chirurgicale réglée ont été aléatoirement répartis en trois groupes égaux. Ceux du groupe I ont reçu 1 g de sulfate de magnésium, ceux du groupe II, 40 mg de lidocaïne à 2 % et ceux du groupe III, une solution saline, tous dans un volume de 2 mL et accompagnés d'une occlusion veineuse d'une minute. L'induction avec 2,5 mg·kg⁻¹ de propofol a été réalisée après la levée de l'occlusion veineuse. La douleur a été évaluée selon une échelle en quatre points : 0 = aucune douleur, 1 = douleur légère, 2 = douleur modérée et 3 = douleur sévère, au moment du prétraitement et de l'injection de propofol. Les résultats ont été analysés par le test «Z». Une valeur de $P < 0,05$ était considérée significative.

Résultats : La douleur du prétraitement iv au magnésium a été de 31 %, et de 2 % pour la lidocaïne et la solution salée ($P < 0,05$). On a noté que 76 % des témoins, mais 32 % et 42 % des patients des groupes magnésium ou lidocaïne, respectivement ($P < 0,05$) ont eu des douleurs à l'injection iv de propofol. La lidocaïne et le magnésium ont une action similaire comme prétraitement de la douleur causée par le propofol ($P > 0,05$).

Conclusions : Les prétraitements intraveineux au magnésium et à la lidocaïne réduisent de façon similaire la douleur induite par le propofol. Mais le prétraitement au magnésium peut lui-même être douloureux. Rien ne justifie donc son usage pour atténuer la douleur associée à l'injection iv de propofol.

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PROPOFOL produces anesthesia with rapid recovery. However, it causes pain or discomfort on injection in 45 to 75% of patients.¹ Among 33 clinical problems, propofol-induced pain ranked seventh, when both clinical importance and frequency were considered.² Adding lidocaine to propofol, cooling or warming propofol, diluting the propofol solution, injecting propofol into a large vein, pretreatment with *iv* lidocaine, ondansetron, metoclopramide, an opioid or thiopental with or without tourniquet have been tried for minimizing propofol induced pain, with variable results.³⁻⁶ Magnesium has also been used to provide analgesia for pain caused by propofol injection.⁷

Magnesium is an antagonist of the N-methyl-D-aspartate (NMDA) receptor ion channel, which may explain, in part, its analgesic activity. Magnesium also has calcium channel blocking activity and many calcium channel blockers have antinociceptive effects.⁸ In this randomized, double-blind, placebo-controlled study using a venous retention technique, we compared the efficacy of magnesium with that of lidocaine for the prevention of propofol-induced pain during induction of anesthesia. We hypothesized that pretreatment with magnesium would be equally or more effective than lidocaine in reducing pain due to propofol injection.

Methods

Following approval by the institution's Ethical Committee and after obtaining written informed consent from patients, this prospective study was conducted in a double-blind randomized fashion. Patients with neuromuscular disease, difficulty in communication, cardiac rhythm other than sinus rhythm, a history of angina or myocardial infarction and endocrine or metabolic disease were excluded from the study.

We recruited 300 ASA physical status I and II adult patients between the ages of 18 and 50 yr undergoing elective surgical procedures. Patients were randomly assigned into three groups of 100 each using a table of random numbers. Patients received pretreatment solutions one minute before induction of anesthesia with propofol 2.5 mg·kg⁻¹. Group I received magnesium sulfate 50% (2 mL), Group II received lidocaine 2% (2 mL) and Group III received normal saline (2 mL). Patients were premedicated with *po* lorazepam 2 mg and ranitidine 150 mg the night before surgery and two hours before the induction of anesthesia. After instituting monitoring with an electrocardiogram, noninvasive arterial blood pressure and pulse oximeter, an 18-gauge cannula was inserted into the dorsum of both hands. One cannula was used for the infusion of *iv* fluids and the other one for the administration of drugs.

An anesthesiologist not involved in the study prepared pretreatment solutions and the investigator was blinded to study drugs. Venous drainage was occluded manually at mid-arm by an assistant and the pretreatment solution given over three seconds. The patients were asked whether they felt any pain during the administration of the pretreatment solution. Venous occlusion was released one minute after the administration of pretreatment. Thereafter, one fourth of the total calculated dose of propofol was administered over five seconds and patients were again asked whether they felt any pain or discomfort during the administration of propofol. A second, independent anesthesiologist who was unaware of group assignment, assessed the level of pain.

Pain was assessed using a four-point scale: 0 = no pain, 1 = mild pain (pain reported only in response to questioning without any behavioural signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning); and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears).⁷

Heart rate, systolic, diastolic and mean blood pressures were recorded before the administration of pretreatment solution (considered as baseline) before laryngoscopy, one and five minutes following intubation. Within 24 hr after the operation, the injection site was checked for pain, edema, or allergic reaction by an anesthesiologist who was unaware of group assignment. Results were analyzed by comparing two proportions by normal approximation ('Z' test). A *P* value of < 0.05 was considered significant.

Results

All three groups were comparable with respect to demographic characteristics (Table I). The number of patients who experienced pain or discomfort with the *iv* injection of pretreatment solutions is shown in Table II. The overall incidence of pain during *iv* injection of pretreatment with magnesium was 31%, compared to 2% in each of the lidocaine and control groups (*P* < 0.05). Pretreatment with magnesium produced mild pain in 21%, moderate in 4% and severe in 6% of patients. The overall incidence of pain during *iv* injection of propofol in the various groups is shown in Table III. In the control group 76% of the patients had pain during *iv* propofol, compared to 32% and 42% in the magnesium and lidocaine groups respectively (*P* < 0.05). Lidocaine and magnesium pretreatments were equally effective in attenuating pain during *iv* injection of propofol (*P* > 0.05). No complications such as pain, edema, or allergic reaction

TABLE I Demographic data

Groups	Age (yr)	Sex (m/f)	ASA class (I/II)	Weight (kg)
Group I magnesium (<i>n</i> = 100)	33.6 ± 15.4	46/54	46/54	58.2 ± 12.4
Group II lidocaine (<i>n</i> = 100)	31.8 ± 14.8	49/51	44/56	56.8 ± 14.8
Group III control (<i>n</i> = 100)	34.5 ± 16.2	44/56	50/50	54.5 ± 11.5

Data is presented as either number of patients or mean ± SD.

TABLE II Assessment of pain during *iv* injection of pretreatment solution

Severity of pain	Group I magnesium (<i>n</i> = 100)	Group II lidocaine (<i>n</i> = 100)	Group III control (<i>n</i> = 100)	Power of the study to detect a difference between magnesium and control
No pain	69*	98	98	99
Mild pain (A)	21*	2	1	99
Moderate pain (B)	4	0	1	---
Severe pain (C)	6*	0	0	70
Pain (A+B+C)	31*	2	2	99

**P* < 0.05 *vs* control.

TABLE III Assessment of pain during *iv* injection of propofol

Severity of pain	Group I magnesium (<i>n</i> = 100)	Group II lidocaine (<i>n</i> = 100)	Group III control (<i>n</i> = 100)	Power of the study to detect a difference between magnesium and control	lidocaine and control
No pain	68*	58*	24	100	99
Mild pain (A)	29*	30*	10	93	94
Moderate pain (B)	3*	10*	36	100	99
Severe pain (C)	0*	2*	30	100	99
Pain (A+B+C)	32*	42*	76	100	99

**P* < 0.05 *vs* control.

were observed at the injection site within the first 24 hr after the operation. No difference was observed in the three groups with regard to heart rate, systolic, diastolic and mean blood pressures recorded at different time intervals.

Discussion

The overall incidence of pain during *iv* injection of propofol in the control group was 76% as compared to 32% and 42% observed in the magnesium and lidocaine groups respectively. Lidocaine and magnesium pretreatments were equally effective in attenuating pain during *iv* injection of propofol. We also observed that the overall incidence of pain during *iv* injection of pretreatment with magnesium was 31% as compared to 2% observed in each of the lidocaine and control groups (*P* < 0.05).

Memis *et al.* reported an 18% incidence of pain following pretreatment with magnesium, which was mild in nature.⁷ The difference with our results may be explained by the number of cases studied or the site of administration of drugs. We included 100 patients in each group and used a dorsal vein of the hand, as compared to 50 patients in each group with the use of brachial vein in the study by Memis *et al.*⁷

Propofol, a frequently used *iv* anesthetic with a rapid onset and a short duration of action, causes pain on injection in 45 to 75% of patients.¹ Propofol belongs to the group of phenols, which can irritate the skin, mucous membranes and venous intima.⁹ It may also activate the kallikrein-kinin system and release bradykinin, thereby producing venous dilation and hyper-permeability, which increases the contact between the aqueous phase of propofol and free nerve endings, resulting in pain on injection.^{3,10}

Various methods have been used for attenuating pain during the *iv* injection of propofol. These include: using larger veins;¹¹ decreasing the speed of injection;¹² injecting propofol into a fast running *iv* fluid;¹² diluting it with 5% glucose or 10% intralipid;¹² prior injection of lidocaine, alfentanil, fentanyl, or pentothal;¹² injecting cold saline at 4°C before propofol or discontinuing fluids during the injection;¹² mixing lidocaine in propofol¹³ and cooling propofol to 4°C.⁵

Lidocaine, a local anesthetic, reversibly blocks peripheral nerve pathways through the action on excitable membranes in the arm.¹⁴ Magnesium is the physiological calcium channel blocker and it probably interferes with calcium channel and NMDA receptors. Calcium is required for the release of various neurotransmitters and substances, implicated in nociceptive pain and inflammation. Thus, the analgesic action of some calcium channel blockers is mediated by an increase in nociceptive threshold resulting from interference with calcium influx.^{7,8} Magnesium also antagonizes NMDA receptors. The NMDA receptors are coupled to ion channels permeable to K⁺ and Ca⁺⁺, which may explain its analgesic activity.¹⁵

We conclude that pretreatment with *iv* magnesium 50% (1 g) and lidocaine 2% (40 mg) are equally effective in attenuating pain during *iv* injection of propofol. However, pretreatment with magnesium itself causes pain and therefore should not be used for attenuating pain associated with the *iv* injection of propofol.

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