Small-dose Ketamine Comparison with Lidocaine in The Prevention of Propofol- Induced Pain

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ABSTRACT

Background : Propofol is a widely used anesthetic agent. Pain at injection site is a common problem. Ketamine has been reported to be effective in reducing propofol- induced pain.

Objective : To compare the efficacy of intravenous preemptive with ketamine 10 mg and lidocaine 40 mg in reducing the frequency and severity of pain due to propofol injection.

Methods : In this prospective, randomized, placebo-controlled, double-blinded study, 210 patients with ASA physical status I–II undergoing elective surgery under general anesthesia were randomly allocated into 3 groups. Group S received normal saline; group L received 40 mg of lidocaine and group K received 10 mg of ketamine. Forty-fire seconds after the preemptive bolus, patients were injected with 2 mg/kg of propofol into the dorsal hand vein. Pain assessment was made 15 seconds after injection of propofol using 4- point verbal rating scale (0 = none, 1 = mild, 2 = moderate, 3 = severe)

Statistical analysis : Analysis of variance (ANOVA), chi – square or Kruskal-Wallis test were used where appropriate for comparing data among the three groups. If ANOVA identified significant differences, LSD test was used for post hoc analysis. P value < 0.05 considered statistically significant.

Results : The overall incidence of propofol injection pain was 77.1% of patients in the control group as compared to 25.7% with ketamine 10 mg and 42.9% with lidocaine 40 mg ($p < 0.001$). However, there were no significant differences between ketamine and lidocaine groups ($p = 0.08$). The incidence of moderate to severe pain was lower in ketamine and lidocaine groups compared with the control group (14.3%, 18.6% and 51.4% respectively).

Conclusion : Pretreatment with ketamine 10 mg and lidocaine 40 mg were equally effective reducing pain during propofol injection.

Keywords : anesthetic, propofol, pain, ketamine, lidocaine

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ประสิทธิภาพของยา ketamine เปรียบเทียบกับยา lidocaine ในการป้องกันอาการปวดจากการฉีดยา propofol

บทคัดย่อ

บทนำ : Propofol เป็นยานำสลบที่นิยมใช้กันอย่างแพร่หลาย แต่ข้อเสียที่พบบ่อยคือ ทำให้เกิดอาการปวดบริเวณที่ได้รับการฉีดยาเข้าหลอดดำ มีการศึกษาพบว่ายา ketamine สามารถลดอาการปวดจากการฉีดยา propofol ได้

วัตถุประสงค์ : เพื่อศึกษาประสิทธิของยา ketamine 10 มก ในการลดอุบัติการณ์และความรุนแรงของอาการปวดจากการฉีดยา propofol โดยเปรียบเทียบกับยา lidocaine 40 มก

วิธีการศึกษา : เป็นการศึกษาแบบ prospective, randomized, placebo-controlled, double-blinded โดยทำการศึกษาในผู้ป่วย 210 รายที่มี ASA physical status I-II ที่มารับการผ่าตัดแบบไม่เร่งด่วนและได้รับการระงับความรู้สึกแบบทั่วไป โดยแบ่งเป็น 3 กลุ่ม ดังนี้ กลุ่ม K ผู้ป่วยจะได้รับยา ketamine 10 มก กลุ่ม L จะได้รับยา lidocaine 40 มก และกลุ่ม S จะได้รับน้ำเกลือ normal saline โดยฉีดนำเข้าหลอดเลือดดำบริเวณหลังมือ 45 วินาที ก่อนจะฉีดยา propofol 2 มิลลิกรัมต่อน้ำหนักตัว 1 กิโลกรัม ประเมินอาการปวดหลังจากฉีดยา propofol 15 วินาที โดยใช้ verbal rating scale 4 ระดับ (0 = ไม่ปวด, 1 = ปวดเล็กน้อย, 2 = ปวดปานกลาง, 3 = ปวดรุนแรง) สถิติที่ใช้ในการศึกษานี้ได้แก่ ANOVA, chi – square และKruskal-Wallis's test เพื่อเปรียบเทียบข้อมูลระหว่างทั้ง 3 กลุ่ม ถ้าการเปรียบเทียบโดยใช้สถิติ ANOVA พบมีความแตกต่างอย่างมีนัยสำคัญทางสถิติ จะเลือกใช้ LSD test สำหรับหาความแตกต่างทางสถิติเป็นรายคู่ โดยถือค่า P value ที่น้อยกว่า 0.05 ว่ามีความสำคัญทางสถิติ

ผลการศึกษา : อุบัติการณ์ของอาการปวดจากการฉีดยา propofol ในกลุ่มที่ได้รับยา ketamine เท่ากับ ร้อยละ 25.7 และกลุ่มที่ได้รับยา lidocaine เท่ากับ ร้อยละ 42.9 ซึ่งพบว่าอาการปวดจากการฉีดยาของทั้งสองกลุ่มนี้ลดลงอย่างมีนัยสำคัญเมื่อเปรียบเทียบกับกลุ่มควบคุม ซึ่งเกิดอุบัติการณ์ของอาการปวด ร้อยละ 77.1 ($p < 0.001$) แต่เมื่อเปรียบเทียบกลุ่ม ketamine กับ lidocaine แล้วประสิทธิภาพในการลดอาการปวดไม่แตกต่างกัน ผู้ป่วยที่มีอาการปวดปานกลางถึงรุนแรงในกลุ่ม ketamine และกลุ่ม lidocaine พบอุบัติการณ์น้อยกว่ากลุ่มควบคุม ร้อยละ 14.3% 18.6% และร้อยละ 51.4% ตามลำดับ

สรุป : การฉีดนำด้วยยา ketamine 10 มก มีประสิทธิภาพเทียบเท่ากับยา lidocaine ในการลดอาการปวดจากการฉีดยา propofol เข้าหลอดเลือดดำ

คำสำคัญ : anesthetic, propofol, pain, ketamine, lidocaine

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Introduction

Propofol is a popular intravenous anesthetic agent providing smooth induction and rapid recovery from anesthesia. However, pain on injection of propofol, which has been reported 28-90%, is a common problem.[1-5] The mechanism of propofol injection pain remains unclear. Scott et al suggested that the pain probably results from a direct irritant or activation of pain mediator such as the kinin cascade system.[1] Various methods have been used to reduce propofol injection pain. The most frequently used method is the use of lidocaine either by mixing it with propofol or by pretreatment with lidocaine.[1-2], [4-13] However, the failure rate of this technique has been found to be 32% to 48%.[1-2], [5-7], [14]

Ketamine, an N-methyl-D-aspatate (NMDA) receptor antagonist, has a local anesthetic action when administered intravenously for regional anesthesia.[15] Ketamine has been recognized one candidate to effective preventing propofol-induced pain.[14], [16-22] Several studies have shown the use of ketamine to be effective. Pre-treatmeat with ketamine 10 mg significantly reduced the incidence of pain to 12% to 28%.[3-4], [7-8]

The aim of this study was to determine the efficacy of intravenous ketamine 10 mg compare with lidocaine 40 mg in reducing the frequency and severity of pain due to propofol injection.

Methods

The study protocol was approved by the local institutional ethics committee and written informed consent was obtained from two hundred and ten patients, age 15-75 years with ASA physical status I-II, undergoing elective surgery under general anesthesia.Exclusion criteria were: patient taking regular analgesics or sedatives, any neurologic or cardiovascular disease and those with allergy to propofol, lidocaine or ketamine. No premedication was given.

Using computer-generated numbers, patients were randomly assigned to one of three groups: Group K was pretreated with ketamine 10 mg add normal saline 1.8 ml, Group L was pretreated with lidocaine 40 mg (2 ml.) and Group S was pretreated with normal saline 2 ml. An anesthetist who was not involved in the research prepared the pretreated drugs. Anesthesia was induced and the data were collected by anesthesiologist who was unaware of the treatment assignment.

On arrival in the operating room, a 20-gauge cannula was inserted into a vein on the dorsum of hand without the use of local anesthetic and continuous infusion with Acetate Ringer's or normal saline solution. Routine monitoring was placed. The study drug was administered without venous occlusion. Forty-five seconds after the pretreatment bolus, propofol 2 ml/kg was

administered at rate 0.5 ml/second. After injection of propofol 15 seconds, pain and severity were assessed by 4-point verbal rating scale (VRS) (Table 1). After assessment of the pain intensity, the remaining dose of propofol was given and anesthesia was continued as planned.

After finished the operation, an experienced nurse in post-anesthesia care unit (PACU) who was blinded to the study, check for abnormal behavioral response including hallucination, illusions, and delirium.

Table 1 Assessment of pain by 4-point verbal rating scale during propofol injection

Pain scale	Severity of pain
0 = none	No pain
1 = mild	Pain reported in response to questioning only, without any behavior signs
2 = moderate	Pain reported in response to questioning and accompanied by a behavioral signs, or pain reported spontaneously without questioning
3 = severe	Strong verbal response accompanied by facial grimacing, withdrawal of the hand, or tears

Analysis of variance (ANOVA), chi – square or Kruskal-Wallis test were used where appropriate for comparing data among the three groups. If ANOVA identified significant differences, LSD test was used for post hoc analysis. P value < 0.05 considered statistically significant.

Results

Patient baseline characteristics were no significantly difference between the three groups. (Table 2)

Table 2 Patient baseline characteristics

	Ketamine (n = 70)	Lidocaine (n = 70)	Normal saline (n = 70)	p-value
Gender				
Male : Female	28 : 42	25:45	30:40	0.68
Age (years)	38.5 ± 14.0	40.0 ± 16.8	39.0 ± 15.0	0.85
Weight (kg)	58.6 ± 8.6	56.8 ± 8.5	58.0 ± 8.9	0.46
Height (cm)	160.5 ± 6.7	160.9 ± 6.3	160.3 ± 6.8	0.83

Data are expressed as number of patients or as mean ± SD.

The overall incidence of pain during propofol administration was shown in Table 3. The incidence of pain in control group was 77.1% as compared to 25.7% in ketamine group and 42.9% in lidocaine group.

Patients in ketamine and lidocaine group had significantly fewer frequency and severity of pain during propofol injection than did patients in control group ($p < 0.001$). The incidence of moderate to severe pain was lower in ketamine and lidocaine groups compared with the control group (14.3%, 18.6% and 51.4% respectively). However, this study demonstrated that efficacy of ketamine 10 mg and lidocaine 40 mg had no significant difference to reduced pain during propofol injection ($p = 0.08$) (Table 3).

Table 3 Incidence and severity of pain during injection of propofol

	Ketamine (n = 70)	Lidocaine (n = 70)	Normal saline (n = 70)
Incidence of pain	12 (25.7) *	30 (42.9) *	54 (77.1)
Pain score			
0 (none)	52 (74.3)	40 (57.1)	16 (22.9)
1 (mild)	8 (11.4)	17 (24.3)	18 (25.7)
2 (moderate)	8 (11.4)	11 (15.7)	22 (31.4)
3 (severe)	2 (2.9)	2 (2.9)	14 (20.0)
Median of pain score	0	0	2

Data are expressed as numbers of patients (%), * $p = 0.001$ compared with normal saline group, but there were no significant difference between ketamine and lidocaine group ($p = 0.08$).

In PACU, emergence reaction such as hallucination or delirium and skin erythema or wheal did not occur in any patients.

Discussion

Ketamine has a local anesthetic effect action when administered intravenously for regional anesthesia.[15] Several studies have shown the use of pretreatment ketamine to be effective reduced pain on injection of propofol.[3-5, 14, 22]

The overall incidence of propofol-induced pain was 25.7% in ketamine group, 42.9% in lidocaine group and 77.1% in control group. This study demonstrated that pretreatment with ketamine 10 mg or lidocaine 40 mg were effective reduction pain on propofol injection more than control. However, there was no statistical difference between ketamine and lidocaine in attenuating pain from propofol injection.

In other similar studies, Tan et al demonstrated that ketamine 10 mg prior to propofol administration without application of tourniquet can reduce pain from 84% to 26%.[3] Batra et al suggested that ketamine 10 mg with venous occlusion as an effective alternative to lidocaine for alleviating pain from propofol injection.[4] Koo et al reported that ketamine 100 μg/kg given just before propofol injection, decreased incidence and severity of pain more effective than small doses of ketamine (10 and 50 μg/kg). Ketamine 100 μg/kg reduced the incidence of pain from 86.7% to 46.7%.[14] The most likely explanation for the differences in the incidence of pain due to propofol injection is the different study protocol used. In the previous study used ketamine 100 μg/kg, while this study used ketamine 10 mg (approximate 150-200 μg/kg). Second reason, the previous study injected ketamine just before propofol injection, while this study was injection of ketamine 45 seconds before propofol injection.

The mechanism of ketamine for attenuation pain associated with propofol injection still not known. The previous studies, they postulated that possible mechanism was the result of a peripheral local anesthetic action that attenuated the afferent pain pathway, rather than activate NMDA receptor in the central system.[3-5] Badrinath et al suggested that combinations of ketamine and propofol provided sedative effect during monitored anesthesia care.[23] In this study, some patients who received ketamine were fell asleep, but all patients were able to response to the investigator. It might the result of the combination of ketamine and propofol have an additive hypnotic effect which decreases pain sensation in centrally. Iwata et al. [22] reported that 1.0 mg/kg of ketamine completely eliminated the pain. They postulated that the central analgesic effect by the larger doses of ketamine might modulate the pain. However, they also found that the high dose of ketamine (0.5-1 mg/kg) was significantly produced more secretions and ketamine high doses could affect emergence from anesthesia after minor surgical procedure.

The optimal dosage and timing of pretreatment ketamine as a means of prevention propofol-induced pain will require further investigation.

Conclusion

In conclusion, both ketamine and lidocaine significantly reduce incidence and severity of pain during propofol injection. If the hand vein is the site of propofol injection, pretreatment 45 seconds with ketamine 10 mg also effective alternative method for reduction pain at injection site.

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