J Korean Assoc Maxillofac Plast Reconstr Surg 2012;34(6):449-454
pISSN:1225-4207 eISSN: 2233-7296
Original Article

A Comparison of the Effects of Concomitant Analgesics with Midazolam for Sedative Dental Therapy

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Abstract

Purpose: Intravenous sedation with midazolam is common in contemporary dentistry. That is effective for anxious patients, but additional analgesic agent needs to be used, because midazolam alone doesn't have an analgesic effect. This study was performed to select an analgesic agent between an opioid agent, and nonsteroidal anti-inflammatory drugs as adjunctives in intravenous sedation with midazolam.

Methods: The subjects were 60 patients who visited the Department of Oral and Maxillofacial Surgery, Sacred Heart Hospital, Hallym University, between August 2009 and February 2010. Conscious sedation was performed on 20 patients of 3 groups (control group, ketorolac group, and fentanyl group), who were divided randomly. The analgesic agent was administrated preoperatively. For sedation, vital signs were recorded. After sedation and operation, subjective questionnaires of the patient and operator were implemented.

Results: All of the SPO_2, blood pressure, and heart rates stayed within the normal range for sedation. The sedation depth and analgesic effect of the ketorolac group and fentanyl group were similar. In the case of sedation depth, 12 patients in the ketorolac group and 14 patients in the fentanyl group had no memory of surgery. In the case of analgesic effect, the visual analogue scale of pain scored 2～3 in 13 patients in the ketorolac group, and 0～2 in 12 patients in the fentanyl group. The satisfaction of patients and doctors was also similar.

Conclusion: Considering the management and complication of an opioid agent, non-steroidal anti-inflammatory drugs is more effective than an opioid agent.

Key words: Analgesic effect, Midazolam, Ketorolac, Fentanyl

Introduction

Intravenous sedative therapy using midazolam (Midazolam injection 5 mg/5 mL, Bukwang Pharm Co., Ltd, Seoul, Korea) is widely used in dentistry. Though the use of midazolam alone as a sedative can provide sedation, decrease in anxiety, and anterograde amnesia, it cannot offer analgesic effect. Thus, the administration of midazolam in combination with narcotic analgesic is expected to be effective for inducing sedative effect[1,2]. As it was reported that, however, the administration of midazolam in combination with narcotic analgesic (Fentanyl Citrate Hana injection 2 mL/A, Hana Pharm Co., Ltd, Hwaseong, Korea) significantly increased the incidence of hypopnea, amnesia, and postoperative cognitive dysfunction, the combination administration of midazolam and narcotic analgesic is not

RECEIVED July 24, 2012, REVISED September 4, 2012, ACCEPTED November 22, 2012

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easy to apply to dental treatment[3,4].

Ketorolac tromethamine (Keromin injection 30 mg/A, Hana Pharm Co., Ltd) is a non-steroidal anti-inflammatory drug (NSAID) injection. This agent is known to have analgesic effect similar to those of morphine and meperidine in moderate to severe pain[5].

The purpose of this study was to identify ketorolac is more effective than narcotic analgesic with midazolam to enhance analgesic and sedation effect in minor surgery such as implant placement or extraction of third molar.

Materials and Methods

1. Selection of patients

Total 60 patients who visited Department of Oral Surgery, Hallym University Sacred Heart Hospital for extraction of third molar or other minor surgeries were included in the study. All the patients classified American Society of Anesthesiologists grade I, and randomly allocated to control (n=20) and two experimental groups (n=40, each group=20).

The control group received sedative therapy using ringer solution and midazolam (0.035 mg/kg) alone and the two experimental groups received ringer solution, and midazolam combination with ketorolac (0.45 mg/kg) or fentanyl (1.4 μg/kg). Most of the surgeries were for extraction of one or more third molars, except one for implant placement in one patient in control group, plate removal in one patient in fentanyl (narcotic analgesic) group, and cyst enucleation in one patient in ketorolac group. The mean age of the control, ketorolac and fentanyl groups were 23.75, 28.05, and 23 years, respectively (Table 1).

2. Sedative therapy protocol

The patients were admitted to the hospital on the day of their surgery. The lactate ringer solution (Hartmann Dex Choonwae Solution 500 mL, JW Pharmaceutical Corporation, Seoul, Korea) was used as the ringer solution, and IV cefazedone (Resposporen, 1 g/vial, 14 mg/kg, Hanall Biopharma, Seoul, Korea) was administered pre-operatively. Since then, the control group received sedative therapy without the administration of any agent, and the experiment group received an IV analgesic prior to the sedative therapy. Fentanyl citrate (Fentanyl Citrate, 2 mL/A, 0.0014 mg/kg, Hana Pharm Co., Ltd) was mixed with 50 mL of saline solution (Normal Saline, 50 mL, JW Life Science, Dangjin, Korea) before it was used, and ketorolac (Keromin, 30 mg/A, 0.45 mg/kg, Hana Pharm Co., Ltd) that was supplied in an ampule was administered intravenously. Before the start of the sedative therapy, the pre-operative oxygen saturation, blood pressure and heart rate were measured. Then 3 L of oxygen was supplied to the patient via his/her nasal cannula while he/she was in a supine position.

A midazolam (Midazolam, 5 mg/5 mL, 0.035 mg/kg, Bukwang Pharm Co., Ltd) one ampule (5 mg) was used, and when operating time was prolonged by 30 minutes or more, or patient awakened, midazolam 2 mL was additionally administered. After intravenous injection of midazolam was completed, vital sign was recorded again. After observing that patient was in sleep state, local anesthesia was performed. Then, vital sign was measured again. All surgeons (5 surgeons) used to same sedative protocols on their surgery. Before and after the planned surgery, vital sign was recorded. Until patient awakened completely, oxygen was supplied for 5 minutes or more via nasal prong, and then operation was ended. After sedative therapy, both patients and surgeons were surveyed. On the day of seda-

Table 1. Patient demographics

Variable	Control group (n=20)	Ketorolac group (n=20)	Fentanyl group (n=20)
Age (yr)	23.75±7.37	28.05±9.59	23.00±6.0
Gender (M/F)	11/9	10/10	11/9
Weight (kg)	60.50±8.84	65.60±15.99	64.80±14.42
Height (cm)	166.60±6.47	169.05±9.35	170.70±8.99
Sedation time (min)	29.20±8.00	43.35±19.25	38.15±11.72
Operation time (min)	19.15±6.96	30.95±17.35	27.90±11.83

Values are presented as mean±standard deviation or number.
M, male; F, female.

tive therapy after recovery from the sedation, pain was graded using visual analogue scale (VAS) ranging from 0∼10 points, and whether patient had memory of the time during sedative therapy was performed was investigated. Satisfaction level 1 day after the sedative therapy was investigated (Table 2).

3. Statistical analysis

Statistical analysis was performed using SPSS Statistic version 17.0 (SPSS Inc., Chicago, IL, USA). Test of normality of the sample was performed using Kolmogorov-Smirnov, Shapiro-Wilk test. The Shapiro-Wilk test is generally known that it is suitable when the sample size is less than 20 for normality test. Age, weight, height, and preoperative blood pressure and heart rate were compared between groups using one-way ANOVA (significance level, $P<0.05$). Comparison of vital signs before surgery and at each phase of sedative therapy was performed using paired t-test (significance level, $P<0.05$). The results of subjective tests of VAS, level of satisfaction, and presence or absence of memory, and response were presented as graphs after analysis of the frequency of relevant outcome. The frequency of oxygen saturation of less than 97% and of more than 97% was analyzed separately.

Results

The mean of age, weight, height and preoperative vital signs were not significantly different between groups. In control group, systolic and usual blood pressure were not significantly different each other.

In case of blood pressure, it significantly decreased in the ketorolac group. It was lowest at the time point of initiation of surgery (P=0.006) and it. The blood pressure decreased during the sedative therapy in the fentanyl group. It significantly decreased immediately after the local anesthesia, and it was lowes at the time point of initiation of surgery (P=0.007) (Fig. 1).

In case of heart rate, In the control group, heart rate showed a pattern of increase after the sedative therapy initiated (P=0.035). It significantly increased immediately after sedation initiated in kerolorac group (P=0.023). It started significantly increasing from the time point of initiation of surgery in fentanyl group (P=0.041) (Fig. 2).

In the investigation on the effect of anterograde amnesia, 10 patients in the control group replied that they had the memory of anesthesia and surgery, whereas 12 patients in the ketorolac group (Fig. 3A, B). In the fentanyl group, 13 patients had no memory of local anesthesia and 14

Table 2. Number of patients recording each score in visual analogue scale analysis

Score	0	1	2	3	4	5	6	7	8	9	10	Total
Control	1 (5)	2 (10)	6 (30)	7 (35)	2 (10)	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	20 (100)
Ketorolac	5 (25)	3 (15)	7 (35)	3 (15)	0 (0)	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	20 (100)
Fentanyl	5 (25)	5 (25)	3 (15)	4 (20)	1 (5)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (100)

Values are presented as number (%).

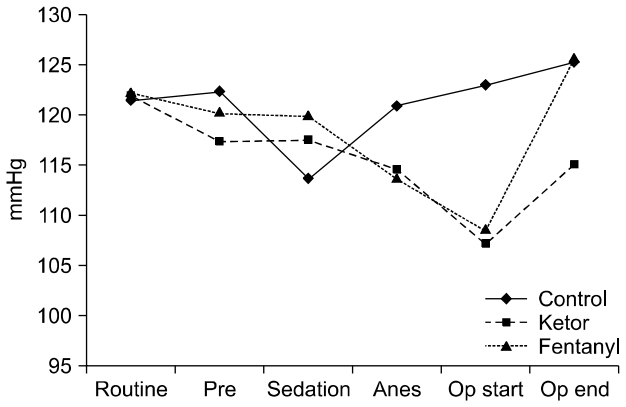

Fig. 1. Shown here are the changes of systolic blood pressure. Data is the mean of each group. Ketor, kotorolac; Pre, pre-sedation; Anes, anesthesia; Op, operation.

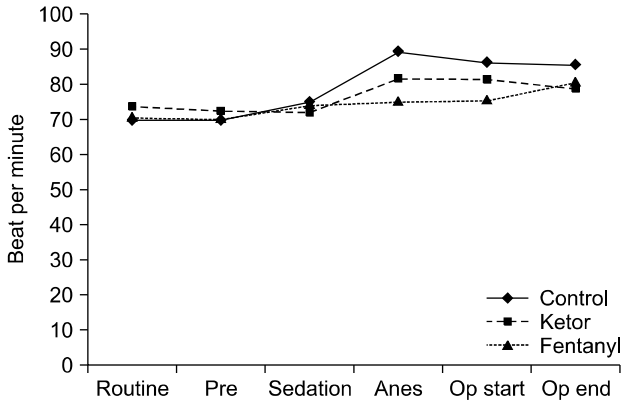

Fig. 2. Shown here are the change of heart rates. Data is the mean of each group. Ketor, kotorolac; Pre, pre-sedation; Anes, anesthesia; Op, operation.

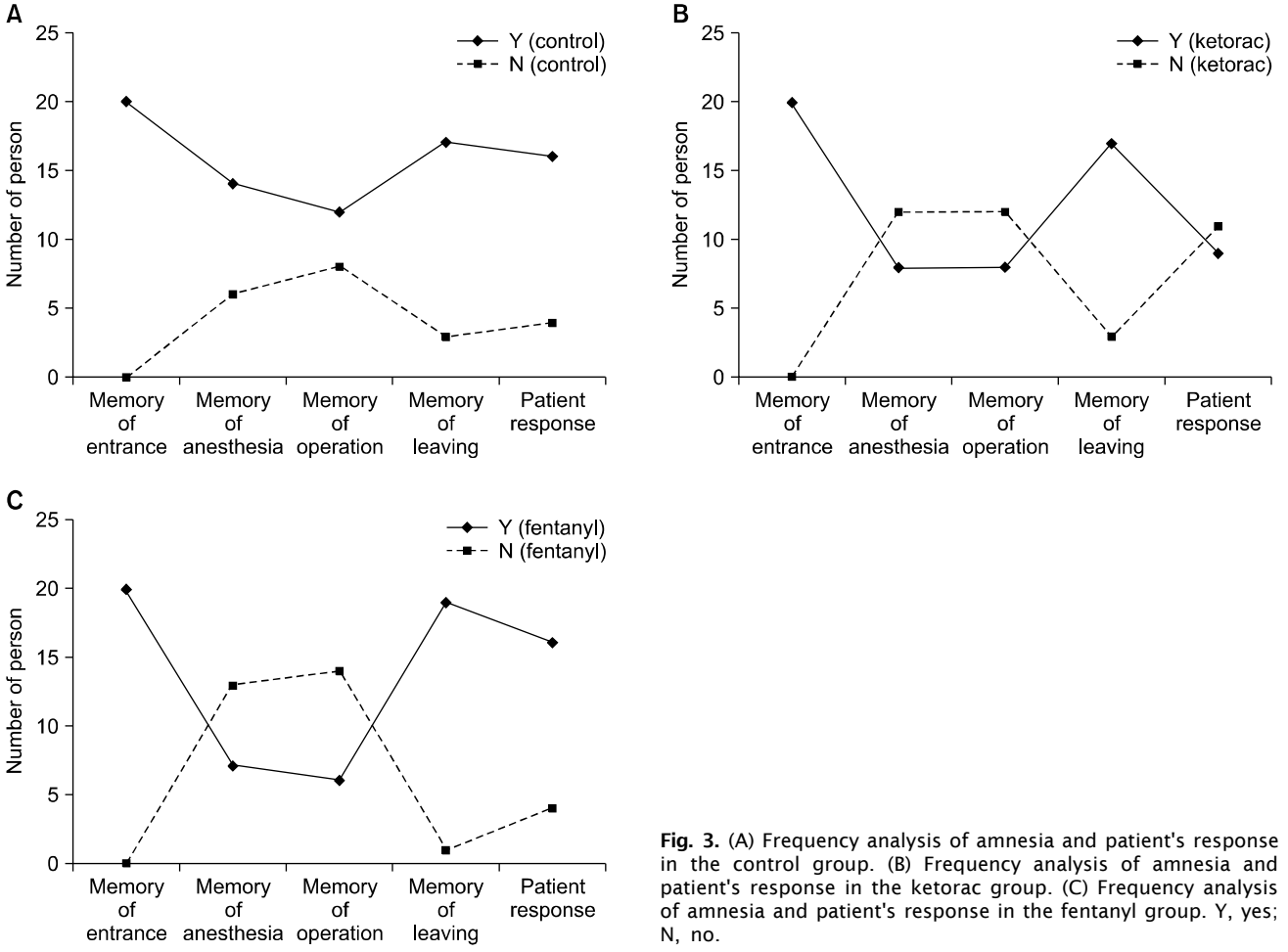

Fig. 3. (A) Frequency analysis of amnesia and patient's response in the control group. (B) Frequency analysis of amnesia and patient's response in the ketorac group. (C) Frequency analysis of amnesia and patient's response in the fentanyl group. Y, yes; N, no.

patients had no memory of surgery (Fig. 3C).

In the investigation on the presence or absence of patient response to the surgeon's verbal command, 4 patients in the control group did not respond to the surgeon's verbal command, whereas 11 patients in the ketorolac group, 4 patients in the fentanyl group.

In the investigation on the VAS of pain, 13 patients in the control group scored 2∼3, 12 patients in the ketorolac group scored 0∼2 and 10 patients in the fentanyl group scored 0∼1.

In the investigation on the patient's satisfaction level, 7 patients chose 'comfortable'; 9, 'slightly uncomfortable', and 4, 'very uncomfortable', in control group; 15 chose 'comfortable', and 2 'very uncomfortable', in ketorolac group; and 14 chose 'comfortable' in fentanyl group (Fig. 4).

In the investigation on surgeon's satisfaction level, positive answer was chosen 16 times in control group, and 18 times in ketorolac group. In fentanyl group, 'satisfactory or above' was chosen 15 times, and 'unsatisfactory' was chosen 5 times (Fig. 5).

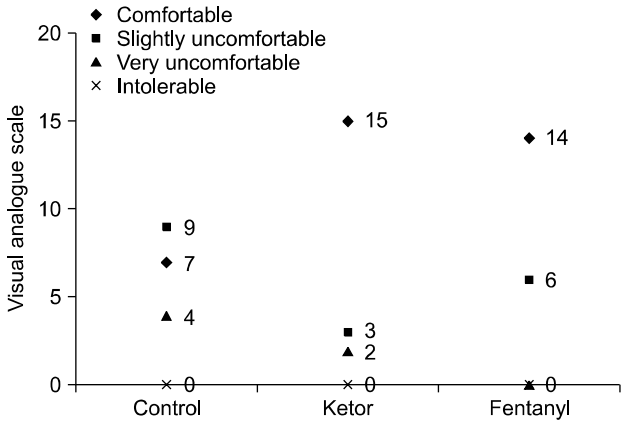

Fig. 4. Frequency analysis of patient's satisfaction. There is no statistical significant difference between ketorolac group and fentanyl group (P=0.09). Ketor, kotorolac.

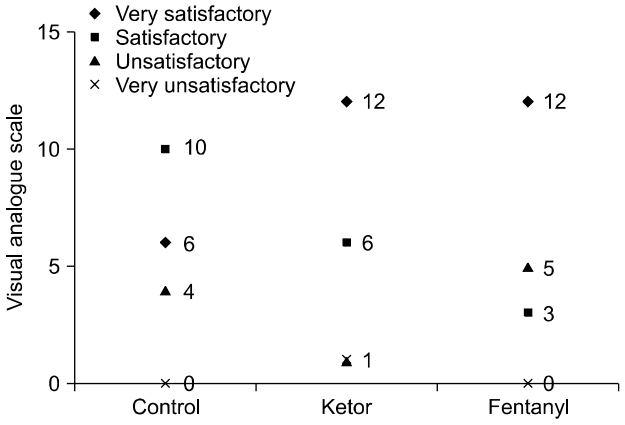

Fig. 5. Frequency analysis of operator's satisfaction. There is a statistical significant difference between experimental and control group (P=0.036). Ketor, kotorolac.

Discussion

Midazolam enhances the inhibitory effect on neurotransmitter by increasing the permeability of cellular membrane for chloride ion by acting on GABA receptors of central nervous system. Through this mechanism, it exerts hypnotic, sedative, atarax, and amnesic effect[6]. Midazolam reaches peak blood concentration within 20 minutes with lasting time of peak blood concentration level of 20～30 minutes, and half-life of 1.5～2.5 hours[7]. It is suitable for use in dental treatment of operating time of 1 hour or less, because of its short half-life, minor effect on cardiovascular, and respiratory system, and anticonvulsion, and muscular relaxation effects[8]. The recommended dose of midazolam for sedation is 0.00025～0.0015 mg/kg/min, mean dose 2.5～7.5 mg, and maximum allowed dose 10 mg[9]. In the present study, bolus injection of midazolam was performed slowly until verrill sign where patient's eyes were half-closed occurred, and maximum dose used was 10 mg regardless of verrill sign. Fentanyl exerts potent analgesic effect 50～100 folds that of morphine, rapid onset of action due to high lipolysis rate, and peak effect within 3～5 minutes after intravenous injection[10].

Injection with fentanyl (0.001 mg/kg) 1～3 minutes prior to the induction of anesthesia can prevent an increase in the blood pressure and tachycardia, and has an inhibitory effect on the motor response[10]. Care must be taken, however, as complications such as respiratory depression, apnea, or bradycardia may occur[11]. To prevent these complications, fentanyl should be injected slowly and intravenously; and in this study, it was mixed with saline solution and injected slowly. Dionne *et al.*[2] (2001) reported that sedative therapy using midazolam in combination with fentanyl was an excellent sedative, had an analgesic effect, and caused no physiological change, though it resulted in temporary hypopnea.

Ketorolac, an NSAID, is used as a post-operative analgesic agent. This agent is a cyclooxygenase inhibitor and inhibits the synthesis of prostaglandin. Generally, though, it is used to relieve moderate or severe pain, it is recommended that ketorolac be used for less than 2 days when it is injected intravenously[12-14]. As for IV sedation, it is commonly used in combination with midazolam. Juodzbalys *et al.*[15] reported that ketorolac, when used in combination with midazolam, was an excellent sedative and had analgesic effects without particular complications. In particular, anterograde amnesia occurred in 80% of the patients in the experiment group.

Although IV sedation using midazolam in combination with ketorolac or fentanyl was shown to have a good sedation effect, no comparative study on it has been performed yet in the field of dentistry. In this study, it was demonstrated based on vital signs that experiment groups were more stable without particular complications than the control group. This indicates that both ketorolac and fentanyl can be used safely if their dose is appropriate and if careful monitoring is provided.

In the investigation on the presence or absence of anterograde amnesia and the response that represented the depth of sedation, the ketorolac group, wherein no sedative effect occurred, showed an effect similar to that of the fentanyl group. This can be interpreted to mean that the analgesic effect of ketorolac alone can sufficiently increase the sedative effect of midazolam. The pain scores based on VAS, were lower in the experiment groups than in the control group. In each group, the highest score was 7, 2, and 1 in the control, ketorolac, and fentanyl groups, respectively, without a marked difference between the ketorolac and fentanyl groups. The level of the patient's satisfaction was higher in the experiment group than in the control group, and similar between the ketorolac and fentanyl group. There is no statistical significant difference between ketorolac group and fentanyl group (P=0.09). The level of the surgeon's satisfaction was slightly higher

in the experiment group than in the control group, and higher in the ketorolac group than in the fentanyl group There is a statistical significant difference between experimental and control group (P=0.036).

Conclusion

Based on the results of this study that the sedative and analgesic effects were better in the ketorolac and fentanyl groups than in the control group, it was concluded that sedative therapy performed in combination with an analgesic would be more effective. The sedative and analgesic effects did not considerably differ between the experimental groups. Thus, it is believed that ketorolac, which is easier to use and safer, is a more suitable combination agent than is the narcotic analgesic, which involves complex drug management and various complications.

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