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Original Article

Remifentanil-Ketamine versus Fentanyl-Ketamine sedation in patients undergoing phacoemulsification with topical anesthesia: comparison of intraocular pressure changes and sedation quality

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Abstract

BACKGROUND: Narcotics and sedatives can reduce intraocular pressure. This study was performed to evaluate the effect of remifentanil plus ketamine on intraocular pressure and sedation quality in comparison with fentanyl plus ketamine during and after operation in patients undergoing phacoemulsification with topical anesthesia.

METHODS: Forty four patients were randomized into two groups to receive either a continuous infusion of remifentanil (0.2 µg/kg/min for 4 min and then 0.1 µg/kg/min: Group R, n=22) or bolus intravenous fentanyl (1.5 µg/kg: Group F, n=22) for sedation. Patients in both groups received low dose ketamine (0.15 mg/kg) intravenously. Topical anesthesia was performed using tetracaine 0.5% eye drop in both eyes. Intraocular pressure was measured in non-operative eye before sedation (baseline), 2 minutes after sedation, before intraocular lens insertion, at the end of operation and 15 minutes after the end of operation using Schiötz tonometer. Sedation, cooperation, satisfaction and pain scores and also postoperative nausea and vomiting were recorded in all patients. Surgeon satisfaction scores were evaluated at the end of operation.

RESULTS: The intraocular pressure did not differ significantly between the two groups throughout the study. The mean (SD) intraocular pressures 2 minutes after sedation, before intraocular lens insertion, at the end of operation and 15 minutes after the end of operation in recovery room were all less than that of baseline in both groups, but the baseline value was decreased only significantly ($P<0.05$) in recovery room [13.75 (3.46) to11.91 (3.43) in group R, respectively and 13.74 (3.05) to11.57 (2.33) in group F, respectively]. The incidence of postoperative nausea and vomiting in group R was higher than that of group F (7 patients in group R and no patient in group F, $P=0.009$).

CONCLUSIONS: Combination of remifentanil infusion and intravenous ketamine did not offer any advantages over the combination of intravenous fentanyl and ketamine in order to prevent intraocular pressure rising during phacoemulsification. The lower incidence of postoperative nausea and vomiting and higher rate of appropriate sedation in fentanyl group suggested fentanyl as a more suitable medication for systemic sedation compared with remifentanil.

KEYWORDS: Fentanyl, remifentanil, intraocular pressure, phacoemulsification, topical anesthesia.

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Management of anesthesia for ophthalmic surgery requires control of intraocular pressure (IOP) perioperatively. An increase in IOP may be catastrophic in patients with penetrating open-eye injury or glaucoma. Control of IOP is important in success of procedures. Most anesthetic and hypnotic drugs reduce IOP [1]. Several studies

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another study, the effect of remifentanil and fentanyl on IOP during the maintenance and demonstrated the role of opioids in attenuating IOP [2-5]. The effect of remifentanil as a new ultra short-acting, mu-selective receptor agonist has been compared with fentanyl in some researches. Remifentanil but not fentanyl has been shown to prevent an increase in IOP after succinylcholine and tracheal intubation [6]. In recovery of anesthesia showed that remifentanil maintains IOP at an equally reduced level with fentanyl. The authors of latter study recommended that further researches should examine the different anesthetic regiments in these clinical settings [7]. Both of those studies were done in patients with non-ophthalmic surgery under general anesthesia. Topical anesthesia for lens extraction in cataract surgery has become increasingly popular [8,9]. Significant increase of IOP during opening of anterior chamber in cataract surgery, similar to penetrating eye injury, may cause damage and loss of vision. Events such as coughing, straining, the Valsalva maneuver or vomiting can cause significant increases in IOP [1]. Sedation can be useful during topical anesthesia in ophthalmic surgery to diminish anxiety and fear associated with the operating room activity and surgical procedures [1,10-12]. Several sedative and analgesic drugs have been used singly or in combination to ensure patient comfort and safety during topical anesthesia [1,9,13-15]. Ketamine in subanesthetic doses produces analgesia while preserve airway patency, ventilation and cardiovascular stability without increasing the IOP [16-18]. It may be added as an adjuvant to sedation drugs for better sedation and analgesia. The aim of this study was to compare the effects of remifentanil plus ketamine on intraocular pressure in non-operative eye, sedation, cooperation, satisfaction and pain scores and also postoperative nausea and vomiting in comparison with fentanyl plus ketamine in patients undergoing phacoemulsification with topical anesthesia.

Methods

Our institution approved the study and written informed consent was obtained from all patients. Forty four patients (40-80 years, ASA I/II) scheduled for elective phacoemulsification were enrolled in this double blind, randomized prospective study. Patients with history of cardiovascular, respiratory and psychiatric disease, reaction to local anesthetics, dependency to narcotics or drug abuse, IOP greater than 20 mmHg, blood pressure less than 90/60 or more than 180/110 mmHg, were excluded from the study. Each patient who needed any surgical or pharmacological intervention out of designed protocol or a patient with operation time longer than 45 minutes was excluded too. Patients were allocated randomly to one of the two groups using the sealed enveloped techniques: group R (Remifentanil, n = 22) and group F (Fentanyl, n = 22). Patients did not receive any premedication. Preoperative preparation and perioperative fluid therapy were the same in all patients. Topical anesthesia was performed using tetracaine 0.5% eye drop in both eyes. All patients were managed by the same anesthesiologist and operated by one surgeon. After preparation of both eyes, drape was done using specified dressing that allowed intraoperative measurement of IOP in non-operative eye in sterile condition. After drape and administration of 8-10 L/min supplemental oxygen via nasal prong, sedation was performed in group R with intravenous infusion of remifentanil (Ultiva®, Glaxo Wellcome Operation, Greenford, UK) 0.2 µg/kg/min (0.2 ml/kg/hr from diluted solution with concentration of 60 µg/ml) for 4 minutes and 0.1 µg/kg/min (0.1 ml/kg/hr) there after. In group F sedation was performed with bolus intravenous fentanyl (fentanyl-Janssen®, Janssen Pharmaceutica, Beerse, Belgium) 1.5 µg/kg (0.03 ml/kg from solution with concentration of 50 µg/ml). In addition, 4 minutes after drape, patients in both groups received low dose ketamine (ketamine hydrochloride®, Rotexmedica, GMBH, Trittau, Germany) 0.15 mg/kg intravenously. For blindness of the study, patients

in group R received intravenous bolus saline solution as the same volume as fentanyl in group F. Conversely, patients in group F received infusion of saline as the same rate as remifentanil in group R. The procedure was performed through a small scleral tunnel incision and the patients lens was emulsified by an ultrasonic probe and then was aspirated. The foldable intraocular lens (IOL) was implanted by an injector. The surgeon who was blinded to sedation techniques measured IOP in non-operative eye using sterile Schiötz tonometer (The Diagnostic Company, Riester, Germany) in supine position. IOP was measured before sedation (baseline), 2 minutes after sedation, before IOL insertion, at the end of operation and 15 minutes after the end of operation in recovery room. Other variables were assessed by the anesthesiologist that was blinded to sedation techniques. Continuous monitoring consisted of electrocardiography (ECG), heart rate (HR), and pulse oximetry (S_pO_2). Respiratory depression and airway patency were assessed using pulse oximetry, chest movement and breathing sounds. Non-invasive blood pressure measurement including systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) and also HR were documented at the above-mentioned time points. Sedation score in all patients was assessed during operation using Ramsay sedation scale, which rates the patients level of arousal as follows: anxious or agitated (level one), cooperative (level two), respond to commands (level three), deep sedation (levels four and five) and unarousable state (level six) [19]. Intraoperative cooperation score was determined by scoring system for patient cooperation, which rates from non-cooperative (level one) to low-cooperative (levels two and three) to good and complete cooperation (levels four and five) [20]. At the end of operation, patients and surgeon satisfaction were determined by scoring system as fallows: 1: bad, 2: fair, 3: good, 4: excellent. Appropriate sedation, cooperation and satisfaction were defined as 2 and 3 in Ramsay scale, 4 and 5 scoring system for patients' cooperation and also 3 and 4 in satisfaction score, respectively. Intraoperative pain intensity was asked from the patients before discharge from the recovery room using visual analog scale (VAS: 0 = no pain, 10 = extreme pain) when they were adequately oriented. We informed all patients about VAS before operation. The occurrence of postoperative nausea and vomiting (PONV) was recorded at recovery room. PONV was treated using intravenous 0.15 mg/kg metoclopramide (Metoclopramide®, Osvah Pharma, Tehran, Iran). For postoperative pain relief, patients received 325 mg acetaminophen oral tablets as their own need. The sample size that was needed to detect a significant difference for IOP between the 2 groups with a 3 mmHg difference, 0.90 power and α error of 0.05 was calculated to be 22. Variables in the two groups were compared using independent t-test for quantitative variables like age, weight, IOP, SBP, DBP, MAP and HR before intervention, Mann-Whitney test for ordered values like cooperation and satisfaction, and chi-square test for nominal variables like ASA class and sex. For comparison of quantitative variables within groups in different situations and between the two groups, ANOVA for repeated measurements was used, taking baseline values as covariate. Paired t-test was used to compare values in different times with baseline values separately. Values for quantitative variables were reported as mean ± standard deviation (SD), and for qualitative variables as count and percent. For all tests, statistical significance was assumed if $P<0.05$. SPSS version 12 was used for statistical analysis.

Results

A total of 44 patients were evaluated in this study. No patient was excluded from the study. Patients' demographic data and baseline IOP, MAP and also HR (before intervention) are shown in table 1. Between the two groups, there was no significant difference in age, weight, sex and baseline data. No significant difference in duration of operation and ASA class between the two groups could be observed. The mean IOP and its changes from

Table 1. Patients demographic data and baseline intraocular pressure, mean arterial pressure and heart rate (before intervention).

Variables	Remifentanil (n=22)	Fentanyl (n=22)
Age (years)	66.2 ± 11.3	66.7 ± 8.8
Weight (kg)	64.0 ± 10.5	69.4 ± 15.3
Gender (m/f)	11/11	9/13
IOP (mmHg)	13.75 ± 3.46	13.74 ± 3.05
MAP (mmHg)	104.1 ± 8.7	103.6 ± 12.1
HR (beats/min)	79.5 ± 19.4	76.6 ± 11.6

Values are mean ± SD or the number of patients.
IOP: intraocular pressure, MAP: mean arterial pressure, HR: heart rate.
There were no significant differences between the two groups.

the baseline value during the study in the two groups are shown in table 2. Data in this table indicates no significant difference between the two groups in order to IOP or IOP changes during the study. In both groups, the mean IOP 15 minutes after the end of operation in recovery room was significantly lower than the baseline value. The highest value of recorded IOP in remifentanil group was 22.4 mmHg 2 minutes after the beginning of sedation and in fentanyl group 18.9 mmHg before insertion of IOL. S_pO_2 remained stable in all patients throughout the study. Surgical complications such as vitreous loss or hemorrhage were not seen during the operation. There was no supplementation out of the study protocol. The mean MAP and HR and changes of those from the baseline values during the study (tables 3 and 4) were not significantly different in both groups. The mean MAP and HR during the study compared with baseline values were not significantly different in each group. The frequency of patients' appropriate sedation, cooperation and satisfaction and also surgeon satisfaction are indicated in table 5. As data shows in this table, the frequency of appropriate patients' sedation in remifentanil was significantly lower than that in fentanyl group. The intensity of intraoperative pain in remifentanil and fentanyl group was 0.27 ± 0.63 and 0.59 ± 1.59, respectively (P = 0.68). Seven patients in remifentanil group and no patient in fentanyl group complained of PONV (P = 0.009). Patients complaining of PONV were treated with a single dose of metoclopramide successfully. In remifentanil group, two patients demonstrated mild muscle rigidity and one patient complained of generalized pruritus; all of them recovered without treatment.

Table 2. Intraocular pressure (mmHg) and its changes from the baseline during the study (mean ± SD).

Time	Remifentanil		Fentanyl	
	IOP	IOP changes	IOP	IOP changes
2 min after sedation	13.35 ± 3.08	-0.39 ± 2.24	13.41 ± 2.48	-0.32 ± 2.14
Before IOL insertion	13.27 ± 3.51	-0.47 ± 3.93	13.88 ± 2.45	+0.14 ± 2.92
End of operation	13.38 ± 3.99	-0.36 ± 4.68	12.41 ± 2.60	-1.32 ± 3.36
15 min after operation	11.91 ± 3.43*	-1.83 ± 3.97	11.57 ± 2.33†	-2.16 ± 2.07

*P = 0.042 vs. baseline value. †P = 0.001 vs. baseline value.
IOP: intraocular pressure, IOL: intraocular lens.

Table 3. Mean arterial pressure (mmHg) and its changes from the baseline during the study (mean ± SD)

Time	Remifentanil (n=22)		Fentanyl (n=22)	
	MAP	MAP changes	MAP	MAP changes
2 min after sedation	104.4 ± 10.3	+0.27 ± 4.99	103.5 ± 10.0	-0.04 ± 6.55
Before IOL insertion	107.7 ± 14.9	+3.63 ± 11.20	105.4 ± 11.3	+1.77 ± 11.14
End of operation	106.9 ± 15.0	+3.23 ± 10.96	104.8 ± 11.4	+0.35 ± 11.26
15 min after operation	99.8 ± 12.4	-4.31 ± 9.67	100.5 ± 13.8	-3.09 ± 14.20

MAP: mean arterial pressure.
There were no significant differences between the two groups.

Table 4. Mean heart rate (beat/min) and its changes from the baseline during the study (mean ± SD)

Time	Remifentanil(n = 22)		Fentanyl(n = 22)	
	HR	HR changes	HR	HR changes
2 min after sedation	79.8 ± 19.8	+0.27 ± 6.64	74.4 ± 11.7	-2.28 ± 4.54
Before IOL insertion	86.5 ± 22.3	+6.95 ± 17.72	78.0 ± 11.9	+2.95 ± 7.74
End of operation	85.6 ± 22.7	+7.42 ± 18.20	76.7 ± 12.6	+0.47 ± 7.35
15 min after operation	77.5 ± 15.0	-2.04 ± 17.68	71.8 ± 10.4	-4.36 ± 7.91

HR: heart rate, There were no significant differences between the two groups.

Table 5. Appropriate sedation, cooperation and satisfaction of patients and surgeon satisfaction

Variables	Remifentanil (n=22)	Fentanyl (n=22)
Patients sedation*	8(36%)	15(68%)
Patients cooperation	16(72%)	19(86%)
Patients satisfaction	19(86%)	20(90%)
Surgeon satisfaction	15(68%)	18(81%)

*P = 0.035, n (%)

Discussion

We performed a prospective, randomized study to compare the effects of remifentanil and fentanyl both in combination with ketamine on IOP and sedation quality in patients undergoing phacoemulsification under topical anesthesia. Our data showed that the combination of remifentanil infusion and intravenous ketamine dose not offer any advantages over the combination of intravenous fentanyl and ketamine in order to prevent IOP rising during surgical manipulation in cataract surgery. Both of the sedation techniques reduced IOP after operation in the recovery room at equal level. No studies have yet compared the effect of remifentanil and fentanyl on IOP in human during cataract surgery at the presence of topical anesthesia plus systemic sedation. Remifentanil, a potent, rapid-acting mu-selective opioid analgesic, is rapidly metabolized by nonspecific blood and tissue esterase. Remifentanil is unique among the currently available opioid analgesics because of its extremely short context-sensitive half-time (3-5 minutes), which is largely independent of the duration of infusion and patients' age [21,22]. Therefore, it is a suitable analgesic for both short and long lasting surgeries especially in elderly patients. Preventing an increase in IOP is an essential goal of anesthetic management in ophthalmic surgery. The use of opioids during induction of anesthesia can help prevent increase in IOP. Remifentanil has been shown to prevent an increase in IOP after succinylcholine and tracheal intubation [2,6]. Sator-katzenschlager and co-workers reported that remifentanil administered as a bolus (1 µg/kg) for non-ophthalmic surgeries under general anesthesia with controlled ventilation, maintains IOP at an equally reduced level compared with fentanyl (2 µg/kg) [7]. Opioids like central nervous system depressants may decrease IOP by their central depressive effect on the diencephalic control of IOP and by facilitating the outflow of aqueous humor from iridocorneal angle [1]. In current study, remifentanil and also fentanyl did not reduce IOP intraoperatively. This difference between the results of these two studies may be due to different anesthetic techniques (general anesthesia vs. light sedation). During controlled ventilation and normocapnia, most anesthetic drugs decrease IOP in proportion to the depth of anesthesia [1]. A significant decrease in IOP was demonstrated in both groups in recovery room compared with baseline values. This reduction of IOP may be due to elimination of surgical stress and attenuation of patients' anxiety during recovery period in this setting. Increase in IOP in early postoperative period (first 24 hours) especially 4

hours after phacoemulsification has been reported. This may be due to closure of the tunnel incision and postoperative inflammatory reaction [23,24]. Frequency of appropriate sedation during operation was significantly lower in remifentanil compared with fentanyl group. There is no study that addressed comparison of remifentanil vs. fentanyl for sedation profile in ophthalmic surgeries. Holas et al compared the effect of remifentanil infusions (0.05 ± 0.03 μg/kg/min), propofol (1.5 ± 0.5 mg/kg/min), and their combination, remifentanil (0.03 ± 0.01 μg/kg/min) and propofol (0.7 ± 0.2 mg/kg/min) for sedation during eye surgery and found better analgesia with remifentanil used as a sole agent [25]. Lacombe et al. evaluated a deep sedation regimen of midazolam 0.03 mg/kg, remifentanil: propofol (1:500) given at an initial propofol infusion rate of 40 μg/kg/min along with fentanyl 1 μg/kg in place of remifentanil in oral surgeries. They found that this remifentanil regimen provided significantly faster recovery and used significantly less propofol compared with the fentanyl regimen [26]. The low frequency of appropriate sedation with remifentanil in our study may be due to unpleasant effects such as rigidity, nausea and pruritus. In this study, the incidence of PONV in remifentanil group was significantly higher than that of fentanyl group. Bekker and colleagues reported that in general anesthesia with remifentanil-nitrous oxide (N_2O), compared with isoflurane-N_2O-fentanyl, the incidence of PONV after remifentanil was insignificantly higher than that of fentanyl [27]. In Bekker's study, elderly patients undergoing spinal surgery were received up to 7 μg/kg fentanyl or 48 μg/kg remifentanil. However, Minkowitz and also Satorkatzenschlager and co-workers found that the incidences of PONV were comparable in remifentanil and fentanyl groups [7,28]. In both studies, patients underwent non-ophthalmic surgeries received infusion of remifentanil (0.25-0.5 μg/kg/min) or an intermittent bolus of fentanyl (2-5 μg/kg) during the maintenance of general anesthesia. These different findings may be related to many risk factors such as anesthetic and surgical risk factors that affect the frequency of PONV in adults [29]. In general, no particular opioid agonist has proved more or less emetogenic than others, but the use of continuous opioid infusion may further increase the incidence of vomiting [30]. The hemodynamic variables were not different in both groups. The dose selection for light sedation in this study did not have any potent cardiovascular effect. We were not able to monitor the end tidal CO_2 during the study period. Unfrequented measurement of IOP in non-operated eye was another limitation of this study.

Conclusions

This study demonstrated that sedation with remifentanil infusion plus low dose intravenous ketamine can prevent IOP rising in non-operative eye during operation and reduce IOP in recovery time similarly to intravenous fentanyl plus ketamine in patients undergoing cataract surgery under topical anesthesia. The lower incidence of PONV and higher appropriate sedation with fentanyl suggested that in patients undergoing cataract surgery under topical anesthesia the use of fentanyl as a systemic sedation may be more suitable than remifentanil.

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