

## Usage of remifentanil and fentanyl in intravenous patient-controlled sedo-analgesia

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### ÖZET

#### Topikal anestezi altında katarakt cerrahisi sırasında intravenöz hasta-kontrollü analjezide remifentanil ve fentanilin kullanımı

Amaç; topikal anestezi altında fakoemülsifikasyon yöntemi ile gerçekleştirilen katarakt cerrahisi sırasında fentanil veya remifentanilin hasta kontrollü sedoanaljezideki etkinliğini araştırmaktır. Prospektif, randomize, çift kör çalışma için etik komite izni alındı. Katarakt cerrahisi geçirecek ASA I-III 120 olgu randomize olarak 3 gruba ayrıldı. Fentanil 0.7 µg/kg yükleme dozu sonrası, 10 µg bolus dozda 5 dakika kilitli kalma süresi, remifentanil 0.3 µg/kg yükleme, 20 µg bolus ve 3 dakika kilitli kalma süresi ayarlanarak hasta kontrollü analjezi (HKA) cihazı ile verildi. Kontrol grubunda serum fizyolojik herhangi bir ilaç katılmadan verildi. Kardiyorespiratuvar sistem bulguları, sözel ağrı skoru ve sedasyon skorları preoperatif, intraoperatif 5., 10., 15., 20. ve 30. dakikalarda kaydedildi. Cerrahi sırasındaki rahatsızlık, HKA cihazına basma ve komplikasyonlar kaydedildi. İlaç verilen gruplarda sözel ağrı skala sonuçları, 15. dakikada kontrol grubundakinden daha düşüktü. Sedasyon skoru; remifentanil grubunda 5. dakikada ( $p=0.019$ ), fentanil grubunda ise 10. dakikada ( $p=0.007$ ) kontrol grubundan anlamlı olarak daha yüksekti. Hasta kontrollü analjezi cihazına basan hasta sayısı kontrol grubunda, ilaç verilen gruplardan anlamlı fazla idi ( $p<0.05$ ). Hasta konforu ve cerrah memnuniyeti ilaç verilen gruplarda daha yüksekti ( $p<0.05$ ). Topikal anesteziye eklenen i.v. hasta kontrollü sedo/analjezinin hasta konforu, cerrah memnuniyeti ve sedoanaljezi için avantaj sağladığı sonucuna varıldı. Hasta kontrollü analjezi özellikle operasyonun başlangıcında anksiyetenin varlığında, healon/lens yerleştirilmesi sırasında uygun ve emniyetli bir yöntemdir.

**Anahtar kelimeler:** Katarakt cerrahisi, fakoemülsifikasyon, topikal anestezi, hasta kontrollü sedo-analjezi, fentanil, remifentanil

### SUMMARY

Our aim was to investigate the effects of patient-controlled sedo/analgesia with fentanyl or remifentanil during cataract surgery with phacoemulsification method under topical anaesthesia. The ethical committee has approved the prospective, randomized, double-blind study. ASA I-III, 120 patients underwent cataract surgery were randomly allocated to 3 groups. Fentanyl was administered in 0.7 µg/kg loading, 10 µg bolus dose with 5 minutes lockout time, remifentanil was administered 0.3 µg/kg loading, 20 µg bolus dose with 3 minutes lockout time by patient controlled analgesia (PCA) equipment. In the control group, saline solution was given without any analgesic drug. Cardiorespiratory system findings, verbal pain scale and sedation scores were recorded preoperatively and intraoperatively at the 5th, 10th, 15th, 20th and 30th minutes. Discomfort during surgery, pressing the PCA button, and complications were recorded. The verbal pain scale scores was significantly lower in the drug groups than the those in control group at the 15th minute. The sedation scores was significantly higher in the remifentanil group at the 5th minute ( $p=0.019$ ) and in the fentanyl group at the 10th minute ( $p=0.007$ ) than those in the control group. The number of patients pressing the PCA button was much higher in the control group than the drug groups ( $p<0.05$ ). Patient comfort and surgeon satisfaction were higher in the drug groups ( $p<0.05$ ). Intravenous-PCA sedo/analgesia addition to topical anaesthesia provides an advantage in sedo/analgesia, patient comfort, and surgeon satisfaction. PCA is a convenient and safe method, especially at the beginning of the operation when anxiety is intense, and during healon/lens implantation.

**Key words:** Cataract surgery, phacoemulsification, topical anaesthesia, patient-controlled sedo-analgesia, fentanyl, remifentanil

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## Introduction

Cataract surgery may be carried out by using general, local/topical anaesthesia, or by a combination of the two methods (Crandall et al. 1999, Janzen et al. 1999, Kothari et al. 1998, Virtanen and Huha 1998, Pac-Soo et al. 1996). Peribulber/retrobulber anaesthesia techniques are invasive, painful and carry risks including retrobulber hemorrhagia, globe perforation, optic nerve damage, respiratory arrest, extended postoperative akinesia, retinal vessel obstruction, ptosis, diplopia, extraocular muscle dysfunction and systemic hypertension (Crandall et al. 1999, Patel et al. 1998, Edge et al. 1993, Hay et al. 1991). Topical anaesthesia has some intraoperative risks including eye movements, incomplete anaesthesia, pain, and toxicity to the cornea/endothelium. Disturbances caused by microscope light and pain may occur during iris manipulation, irrigation and aspiration, and lens implantation (Patel et al. 1996, Hay et al. 1991).

During cataract surgery deep sedation and sudden movements should be prevented, and patients should not be anxious (Pac-Soo et al. 1996, Patel et al. 1996). Benzodiazepines, i.v. induction agents, and opioids have been used for sedo/analgesia to prevent deep sedation and sudden movements (Peacock et al. 1998, Gold et al. 1997, Mackenzie 1996, White and Negus 1996).

Intravenous patient-controlled analgesia (PCA) can be used to relieve pain related to insufficient analgesia due to regional/local or topical anaesthesia, and it also contributes to sedation by relaxing the patient.

Fentanyl is an opioid and may be used for sedation/analgesia in patients undergoing local or topical anesthesia (Balkan et al. 2004, Aydin et al. 2002, Patel et al. 1998).

Remifentanyl affects rapidly because of its short half-time (1.5 min). Like other  $\mu$ -opioids, remifentanyl may cause respiratory depression related to the dosage (Sebel et al. 1995).

Psychomotor function disorders following the surgery are described as postoperative cognitive dysfunction (POCD). The mechanism of POCD is unknown, but anaesthetic drugs, adjuvant drugs (steroids, anticholinergic agents etc), age, infection, existing cognitive disorder and type of surgery may be causes. The Mini Mental Test (MMT) and Short Cognitive Examination (SCE) are commonly used during early or late postoperative

period to measure cognitive functions (Oguz et al. 2003, Breslin et al. 2001, Doods and Allison 1998).

We evaluated the effect of intravenous patient controlled sedoanalgesia (IV-PCSA) with fentanyl and remifentanyl on sedo/analgesia, postoperative cognitive functions, and changes in the cardiorespiratory system, patient comfort, and surgeon satisfaction during cataract surgery with phacoemulsification method under topical anaesthesia.

## Material and Method

The study was performed in a prospective, randomized, double-blind manner with the approval of local ethics committee. An informed consent was obtained from all patients. One hundred twenty patients aged between 50-85 years who had cataract surgery under topical anaesthesia were included in the study.

Exclusion criteria were an excessive blink reflex during intraocular pressure measurement by Goldman applanation tonometry, insufficient pupillar dilatation, posterior synechia, previous glaucoma, nystagmus, congestive heart failure, renal or hepatic insufficiency, respiratory disorders, allergy to fentanyl or remifentanyl, chronic use of alcohol or opioid, insufficient cooperation and low arterial blood pressure.

A list had been created where the numbers from 1 to 120 were randomly assigned to one of the three groups by drawing lots. The patients were put on the list in order of recruitment. The statistical power of the matched analysis was computed in a pilot study performed prior to this study (20 cases in each group). It was observed that the verbal pain scale (VPS) scores and sedation scores (SS) changed clinically and significantly by 70% in the pilot study. Based on the estimates, a sample size that would permit type I error of  $\mu=0.05$  and power of 90% was calculated. Enrolment of 40 patients in each group was found to be sufficient.

One hour before the surgery topical cyclopentolate hydrochloride 1%, tropicamide 1% and phenylephrine hydrochloride 10% drops were instilled three times at 15 minutes intervals. Oxybuprocaine hydrochloride 0.4% drops were instilled for topical anaesthesia 15 minutes before surgery. A sponge soaked in equally by lidocaine 2% (Aritmal®, Adeka) and bupivacaine 0.5% (Marcaine®, Eczacıbasi) was inserted previously into the upper and lower fornices, and removed before surgery. When the surgery lasted more

than 30 minutes, an additional anaesthetic drop was instilled.

An anaesthesiologist evaluated all patients preoperatively and prepared drugs that were administered by PCA equipment. A second anaesthesiologist who was unaware of the groups performed the intraoperative evaluations. Patients' cognitive functions were evaluated preoperatively with short cognitive examination by an anaesthesiologist who was unaware of treatment group the patient was in.

Before the surgery, patients were instructed about the VPS (0=no pain and 10=worst pain imaginable) and how to use the PCA equipment (Pain Management Provider, Abbott Laboratories and Eczacibasi-Baxter, Ireland)

Patients were randomly divided into three groups. Remifentanyl or fentanyl were prepared in the 100 ml medifleks bags that included saline (1 µg/ml and 2 µg/ml for fentanyl and remifentanyl respectively). The first group (fentanyl group) consisted of 40 patients; fentanyl (Fentanyl, Janssen) was administered by PCA equipment in 10 µg bolus doses with a lock-out period of 5 min following an i.v. loading dose of 0.7 µg/kg in 2 ml saline. The second group (remifentanyl group) consisted of 40 patients; remifentanyl (Ultiva-Glaxo Welcome) was administered in 20 µg bolus dose with a lock-out period of 3 min following an i.v. loading dose of 0.3 µg/kg in 2 ml saline. The control group consisted of 40 patients and saline was administered in 10 ml bolus dose with a lock-out period of 5 min following an i.v. loading dose of 2 ml saline without any analgesic drug by PCA equipment.

Cardiopulmonary parameters such as systolic, diastolic and mean arterial pressures (SAP, DAP and MAP), heart rate (HR), peripheral oxygen saturation, end-tidal CO<sub>2</sub> and respiratory rate were monitored during the surgery. VPS and SS were also measured preoperatively and intraoperatively at the 5th, 10th, 15th, 20th and 30th minutes by a second anaesthesiologist. Cardio-respiratory changes were measured by Datex-Ohmeda anaesthesia equipment (AS/3, Datex®, Helsinki, Finland) while patients were oxygenated nasally at a rate of 3 l/min.

Discomfort related to the operating microscope light was evaluated on an absent or present basis. The second anaesthesiologist evaluated anxiety, patient comfort and surgeon satisfaction, the number of times the PCA button was pressed, and intra/postoperative complications. While giving

oxygen to one nasal orifice, the other orifice was connected to the anaesthesia machine to measure ETCO<sub>2</sub>.

Respiratory depression was evaluated as number of respirations <8/minute, O<sub>2</sub> saturation <90 % longer than 30 seconds or apnea longer than 20 seconds. Hypotension was evaluated as a decrease of more than 20 % of beginning blood pressure or MAP<70 mmHg. Bradycardia was evaluated as HR <45/minute. Vertigo, pruritus, vomiting-nausea, chest wall rigidity were determined as complications.

Sedation was evaluated using the Ramsey Scale on which (Wilson et al. 1990); 1=patient is fully awake and answers the questions clearly; 2=awake but with a tendency to sleep; 3=sleeping but can be awakened by verbal stimulation; 4= cannot be awakened by verbal stimulation, responsive to painful stimulation; and 5=cannot be awakened even by painful stimulation.

Anxiety was established by asking "Do you feel anxious or normal?" and the answers were determined as "yes" when patients were anxious or "no" when patients were not anxious. Patient comfort and surgeon satisfaction were assessed as 1 (poor), 2 (moderate), 3 (good), or 4 (perfect). Evaluation of POCD was realized preoperatively and in the postoperative early period; orientation, attention, memory, general knowledge, and near memory with 40 points of The Short Cognitive Examination (Oguz et al. 2003). If any patients became too distressed, it was planned that 0.5 mg/kg fentanyl or 0.2 mg /kg remifentanyl were given for sedo/analgesia.

#### Statistics

The differences in demographic data, duration of surgery, cardiorespiratory parameters, VPS scores, SS, cognitive functions, patient comfort, and surgeon satisfaction between the groups were compared by variance analyses (ANOVA). If there was any difference between the groups, the Bonferroni test was used to determine the groups that had difference. Comparison within the groups was analysed with paired Student's t test. Sex, ASA, discomfort related to microscope light, implantation of the lens and administered of healon, anxiety, the number of times the PCA button was pressed, and complications were assessed by Yates and Fischer's chi-square test. A *p* value less than <0.05 was considered significant.

**Table 1:** Demographic data and duration of surgery.

	<b>Group Fentanyl (n=40)</b>	<b>Group Remifentanyl (n=40)</b>	<b>Group Control (n=40)</b>
Mean age (year) *	66.8±8.1	65.2±9.9	68.6±8.0
Mean height (cm) *	161.9 ±8.6	166.1±9.2	165.1 ±8.4
Mean weight (Kg) *	70.4±11.7	73.1±13.3	72.8±10.9
Gender (M/F)	16/24	26/14	22/18
Duration of surgery (min) *	34.1±8.8	34.4±10.5	32.50±8.9

\*: Mean±SD

## Results

There were no statistical differences in demographic data and duration of operation (Table 1). Sedation scores and verbal pain scale score are shown in Figure 1 and 2.

Diastolic arterial pressure was higher in the control group than in the fentanyl group at the intra-operative 10th, 15th, 20th, 25th, and 30th minutes ( $p=0.009$ ,  $p=0.016$ ,  $p=0.007$ ,  $p=0.003$ ,  $p=0.002$  respectively). Mean AP was lower in the fentanyl group than in the control groups at the 30th minute ( $p=0.017$ ).

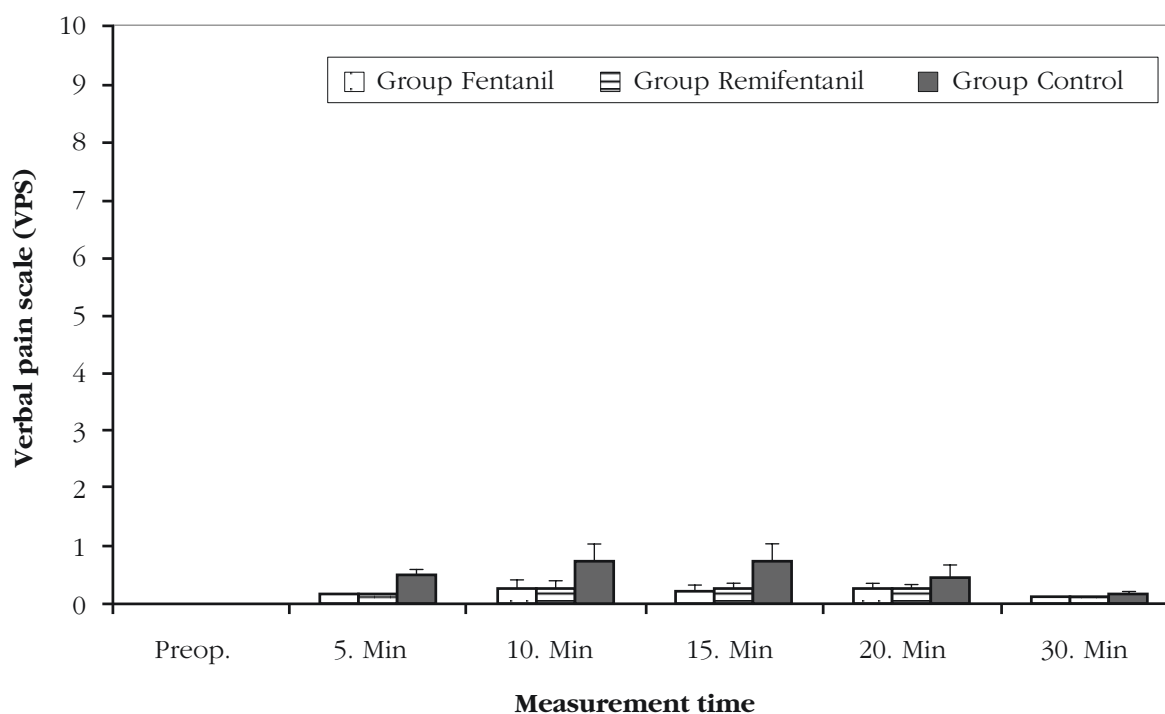
End-tidal CO<sub>2</sub> values were significantly higher in the fentanyl group than in the control group at the 5th and 15th minutes ( $p=0.026$ ,  $p=0.032$

respectively). Respiration rates at the 20th minute and SpO<sub>2</sub> at the 5th minute were lower in the remifentanyl group than in the control group ( $p=0.015$ ,  $p=0.025$  respectively).

Anxiety was similar between the groups ( $X^2=0,497$ ). Surgeon satisfaction was lower in the control group ( $3.65±0.4$ ) than in the fentanyl ( $3.83±0.5$ ) and in the remifentanyl ( $3.87±0.2$ ) groups ( $p=0.02$ ,  $p=0.037$  respectively). Patient comfort was  $3,97±0.2$  in the remifentanyl and in the fentanyl groups while it was  $3,77±0.3$  in the control group ( $p=0.005$ ).

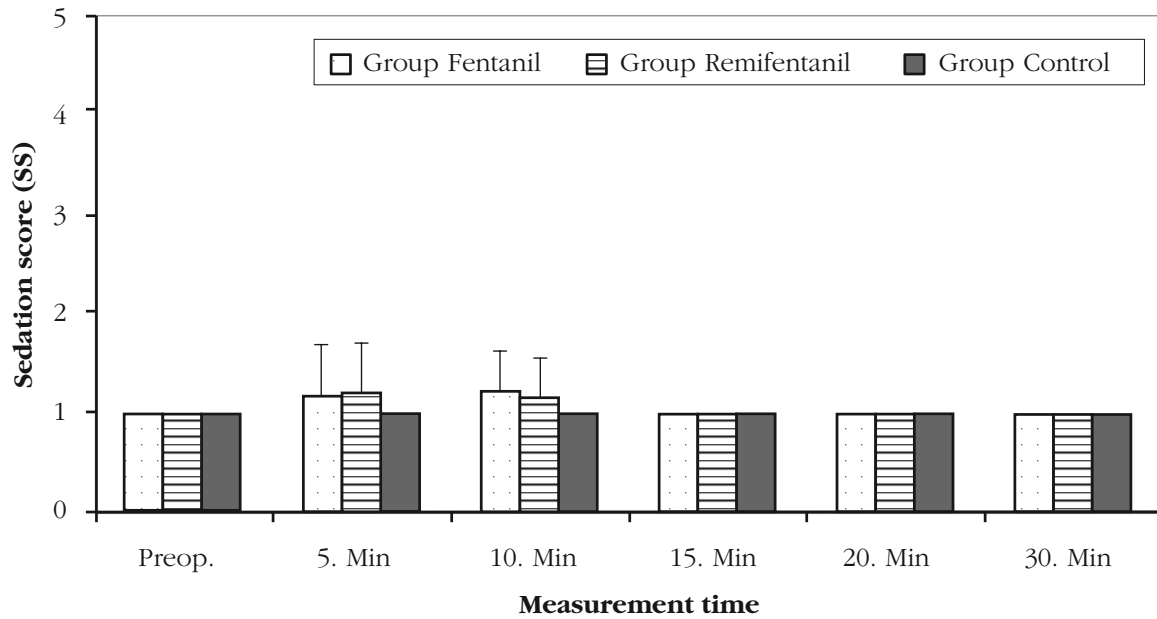
Patients pressed the buttons for additional analgesia a mean of  $1,07±0.5$  times in the fentanyl group,  $1,2±0.6$  times in the remifentanyl group and

**Figure 1:** Verbal pain scores in the groups.



\*: Verbal pain scores in the control group compared with fentanyl and remifentanyl groups at 15. min ( $p=0.014$ ,  $p=0.021$  respectively)

**Figure 2:** Sedation scores in the groups.



\*: In remifentanyl group compared to control group  $p=0.019$ ,  
 \*\*: In fentanyl group compared to control group  $p=0.007$

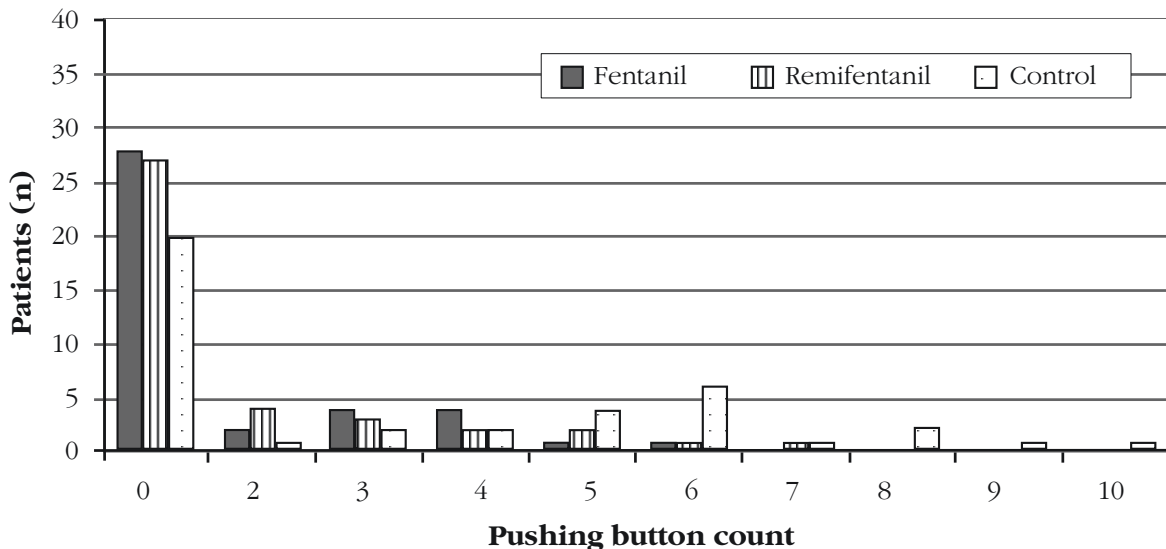
2,85±1.3 times in the control group. The difference between the control group and the fentanyl and remifentanyl groups was significant ( $p=0.004$ ,  $p=0.009$  respectively), (Figure 3). Three patients in the each of drug groups and 6 patients in the control group indicated discomfort from the microscope light ( $X2=0,43$ ). Eight patients in the each of remifentanyl, fentanyl groups, and 13 patients in the control group felt discomfort during implantation of the lens ( $X2=0,32$ ). Four patients in the fentanyl group, 5 patients in the remifentanyl group, and 7 patients in the control group were uncomfortable while receiving healon

( $X2=0,60$ ). There was no complication and POCD difference in the groups. A P value less than  $<0.05$  was considered significant for X2 test.

### Discussion

Cataract surgery with topical anaesthesia in an outpatient manner is increasing day by day (Kuvaki et al. 2000, Kothari et al. 1998, Patel et al. 1998, Patel et al. 1996). Topical anaesthesia is as effective as retrobulbar/peribulbar anaesthesia for cataract surgery in carefully selected patients (Yepez et al. 1999, Virtanen et al. 1998, Patel et al. 1996). Seventy percent of patients in the fentanyl

**Figure 3:** The number of patients pressing the PCA button for analgesia in the groups.



group, 67,5% of patients in the remifentanil group, and 50% of patients in the control group did not press the button for pain treatment, similar to other studies (Janzen et al. 1999, Pac-Soo et al. 1996). Similarity in sedation among the groups can be related to the administration of bolus fentanyl or remifentanil at the beginning of the surgery.

Anxiety and movement of patients occur in patients undergoing peribulbar/retrobulbar or topical anesthesia due to fear of surgery, anxiety of inadequate analgesia and injection pain (Robb and Hargrave 1997, Mulroy 1996). Kothari et al. (1998) reported that, the most important disadvantage of local anaesthesia is anxiety and this problem can be solved by anxiolytic drugs. During topical anaesthesia analgesia and sedation may be required (Kuvaki et al. 2000). However, the level of sedation should not disrupt the cooperation of patients by causing disorientation, uncontrolled movements, and/or loss of integrity of the airway (Janzen et al. 1999, Hampl et al. 1996). Anxiety was similar between the 3 groups. Janzen et al. (1999) reported in their study that 70% of patients pressed the button for sedation, 90% of patients considered patient-controlled sedation (PCS) as useful, and PCS decreased anxiety.

It has been reported that anxious and incooperative patients can decrease surgical quality. In fact, communication with patients has vital importance for the success of topical anaesthesia and surgery. Patient selection must be made more carefully especially as the surgeon just begins to apply topical anaesthesia (Yepez et al. 1999, Edge and Nicoll 1993). Pac-Soo et al. (1996) used the PCS method in their study and reported that in 17 out of 26 (65.3%) patients, sedation was sufficient and elderly patients could use patient-controlled sedation during cataract surgery to induce and maintain anxiolysis and conscious sedation.

There is no accumulation and side effects in patients using remifentanil, nevertheless, effective analgesia has rapid onset and metabolism, so that it can be preferred for elderly patients under monitored conscious analgesia and sedation (Servin et al. 1999). Some surgeons do not prefer deep sedation owing to the risks of disorientation, uncontrolled movements and disappearance of respiratory integrity (Janzen et al. 1999, Hampl et al. 1996).

Holas et al. (1996) determined that 90% of patients obtained sufficient analgesia and sedation without influence of respiration with i.v. remifen-

tanil. Kararmaz et al. (2002) reported that remifentanil was effective and showed no dose-dependent side effects such as respiratory depression, vomiting/nausea during lithotripsy by extracorporeal shock waves. Although, Joo et al. (2001) observed that 15% of patients experienced transient apnoea and desaturation with remifentanil, and when propofol was combined, this rate increased to 52%. In our study, it was planned that the bolus dose of remifentanil to be 0,5 mg/kg. Respiratory depression (respiration rate<8, SpO<sub>2</sub><90%) occurred in 3 patients during pre-study phase, so that bolus dose was decreased to 0.3 mg/kg.

Patel et al. (1998) determined that after topical anaesthesia with 1 µg/kg fentanyl+0.015 mg/kg midazolam, the VPS mean value was 0.78 and 31 of 48 (68.8%) of patients had no intraoperative pain, which are also similar to the results of our study.

In the study of Aydin et al. (2002), patients pressed the button 2.6±3.9 times in the control group and 0.9±1.6 times in the fentanyl group for additional analgesia ( $p=0.025$ ). They observed that, intraoperative additional analgesic was 32.4% (11/33 patients) in the fentanyl group and 50.0% (17/33 patients) in the control group ( $p=0.22$ ).

Inan et al. 2003 observed in their study that fentanyl reduced pain scores significantly during cataract surgery, and the results suggest that fentanyl preemptively decreases injection and intraoperative hyperalgesia.

Cook et al. (1993) explained that giving sedation control from the anaesthetist to the patient may increase safety. We also have the same opinion that, as it supplied a minimal dose of the drugs, self administration of pain and sedation control provides an advantage.

There was no significant difference in SAP, and in DAP between the control and remifentanil groups, and we explained this by a lower dose of remifentanil.

In the study of Rudkin et al. (1992) which included administration of fentanyl+midazolam; there were no cardiovascular- respiratory changes in all groups, and SpO<sub>2</sub> was over 97% in all groups. In our study SpO<sub>2</sub> was also over 95%.

During cataract surgery, because of the face cover, patients continuously breath same air and the inspired CO<sub>2</sub> (FiCO<sub>2</sub>) levels measured by ETCO<sub>2</sub> regularly increase. Increased ETCO<sub>2</sub> and

FiCO<sub>2</sub> affect the patient's anxiety negatively. In our study, ETCO<sub>2</sub> values did not increase during surgery contrary to similar studies (Aydin et al. 2002). It has been thought that the reason for ETCO<sub>2</sub> values not increasing was related to the surgeons' different technique of covering the patient. A shield was located towards the neck level a little bit far from the chin and the covers were passed over this, so breathed air was removed from the field and re-breathed air was aspirated.

Patel et al. (1998) reported that under topical anaesthesia, at about 91% of patients' cooperation was good and excellent, 5/45 (11.1%) of patients had minimal discomfort from the microscope light. In our study discomfort from the microscope light would not bother the patients, and by decreasing strength of light this probable problem was solved.

It has been reported however, that topical anaesthesia supplied sufficient anaesthesia conditions and patient comfort (Patel et al. 1998). Fukasaku and Marron (1994) reported that during cataract surgery under topical anaesthesia discomfort would occur during iris manipulation, and analgesic drug requirement was much more in topical anaesthesia than peribulbar anaesthesia.

In conclusion, during the cataract surgery with the phacoemulsification method, addition of fentanyl or remifentanyl with i.v.-PCA to topical anaesthesia provides an advantage at 10-20 minutes when painful processes are done. Remifentanyl and fentanyl has significantly and similar sedoanalgesic effect during cataract surgery under topical anaesthesia. It can be an appropriate and safe method at the beginning of an operation when anxiety is maximum. Furthermore it was discovered that fentanyl and remifentanyl used in patient-controlled sedo-analgesia increase the comfort of the patients and satisfaction of the surgeons.

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