ORIGINAL ARTICLE

Effect of fentanyl versus buprenorphine on the pupil size in phacoemulsification cataract surgery

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ABSTRACT

Background: Despite several recent innovations in phacoemulsification surgery, importance of pupil diameter in this surgery is becoming more evident. **Purpose**: To compare the effect of opioid agonist (fentanyl) versus opioid agonist–antagonist (buprenorphine) on pupil diameter in cataract surgery and to choose the best opioid in high-risk phacoemulsification surgery. **Methods:** In this randomized double-blinded clinical trial, 60 patients who were candidates for elective phacoemulsification surgery were randomly divided into two equal groups: experimental (buprenorphine, 0.3 μg/kg) and control (fentanyl, 1 μg/kg). Pupil diameter was measured preinjection and at several times postinjection. Blood pressure was recorded at several intervals, as well as shivering, nausea and vomiting, and recovery time. **Results:** Mean (SD) recovery time was significantly less in the control group (19.46 ± 5.43) than in the experimental group (33.23 ± 10.75) ($P < 0.0001$). The constriction effect (ie, pupillary diameter in mm) was significantly lower in the experimental group (0.53 ± 0.45) than in the control group (1.06 ± 0.52) ($P = 0.0001$). The percentages of constriction effect in experimentaland control groups were 7.68% and 15.07%, respectively. The eye was two times more constricted in the control group in comparison with the experimental group after induction of anesthesia. **Conclusion:** Buprenorphine is a better solution to decrease pupil constriction in comparison with fentanylinhigh-risk phacoemulsification surgery.

Key words: *Opioid agonist, opioid agonist-antagonist, buprenorphine, fentanyl, phacoemulsification surgery, pupil constriction*

INTRODUCTION

Despite several recent innovations in phacoemulsification surgery, importance of pupil diameter is becoming widely recognized and handling a patient with small pupils is always challenging.[1-5] Although majority of phacoemulsification surgeries take place under regional anesthesia, there are specific risks associated with local anesthesia for intraocular surgery.

The advanced age and poor state of health of many patients in this group, glaucoma, any previous intraocular surgery, miotic drop consumption, uveitis, ocular trauma, and patient refusal are some contraindications to use local anesthesia in these surgeries.[6-8]

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On the other hand, anesthesiology is dependent on the use of opioids in anesthesia in order to balance anesthetic induction and maintain homodynamic stability.

This is due to this fact that a lot of patients who are candidate for phacoemulsification surgery are elderly and usually have concomitant cardiovascular disorders and are prone to ischemic heart attack.[9-13]

Opioid agonists such as morphine, codeine, fentanyl, and opioid agonist–antagonists, such as buprenorphine and pentazocines, have a miotic effect and decrease the pupil size.[14-22] Opioid agonists are μ-opioid receptor agonistsand opioid agonist–antagonists are μ-antagonists and have full or partial agonist effects at the k-receptor. Buprenorphine is a partial agonist at the μ-receptor.[23-25]

The aim of this study was to compare the pupillary constriction effect of single dose of fentanyl and

buprenorphine in phacoemulsification cataract surgery. We also tested the hypotheses that if a single dose of fentanyl versus buprenorphine makes less pupillary constriction in phacoemulsification cataract surgery. (The primary endpoint was the change in pupil diameter and the secondary endpoints were recovery time and hemodynamic changes, including changes in heart rate, systolic blood pressure, and diastolic blood pressure.)

METHODS

This randomized double-blinded clinical trial was conducted between December 2009 and December 2010 in the educational hospitals of Bushehr University of Medical Sciences, Bushehr, Iran. This study was approved by the Ethics Committee of Bushehr University of Medical Sciences and is registered at ClinicalTrials.gov database (reference no. IRCT201008211936N4). This study was performed according to the requirements of the Declaration of Helsinki.

The medical records of 60 patients who underwent elective phacoemulsification cataract surgery under general anesthesia were reviewed. They were randomly divided into two groups by random drawing of sealed envelopes. All of them underwent physical examination and preclinical tests to rule out any other concomitant disorders.

Exclusion criteria consisted of having history of hepatic or renal disease, contraindication to use fentanyl or buprenorphine, opioid addiction, any health condition that made measuring of the pupil size difficult and all conditions and medications that affect pupil dilatation, including diabetes mellitus, pseudoexfoliative syndrome, peripheral iridotomy, posteriorsynechia, acute or chronic use of alpha-adrenergic agents, and use of atropine-like drug.

Each patient was required to undergo a preoperative ophthalmic examination and none of them had a major refractive error. The patients were asked to refrain from taking any opioids and some other opioid-like drugs for 72 h prior to the surgery. The medications were prepared by an anesthesiologist who was not involved in this study. All therapeutic interventions were standardized.

The routine monitoring was designed to be entirely identical in both the study groups. All the patients in both experimental and control groups were catheterized with IV line 22-gauge and received 500 mL of normal saline solution before induction of anesthesia. They also received fourdrop sets containing cyclopentolate 1% and phenylephrine 2.5% eye drops and 5 min after the last set, pupil measurement was done.

In the control group, the inducible drug was thiopental sodium (4 mg/kg) plus atracurium (0.2 mg/kg) and fentanyl (1 μg/kg). In the experimental group, the inducible drug was thiopental sodium (4 mg/kg) plus (0.2 mg/kg) atracurium and buprenorphine (0.3 μg/kg). All patients in both the groups were given a premedication with 1 mg of IV midazolam, and in order to have a normal $PaCO_2$, the tidal volume and respiratory rate were kept at 10 mL/kg and 10 per min, respectively. It is of note that the FiO_2 in both the groups was the same (50%). All patients were ventilated by Laryngeal Mask Airway through the surgery.

All patients were operated by one surgeon who was blinded to the study. All operations were performed via three entrance sites; one main incision at the temporal side (3.2 mm) for phaco probe and two stab incisions at 6 and 12 O' clock positions for secondary instrument and irrigation and aspirationinstrument.

Maintenance of anesthesia in both the groups was accomplished by using IV infusion of propofol and atracurium, if needed. All the patients were transferred to the recovery room and routine monitoring was done. After using mydriatic drop and prior to the induction of anesthesia, the pupil diameters of patients were measured several times by using portable hand-held pupillometers and this measurement was used as a baseline value. Further measurements of pupil diameter were then made at several times before incision and at the end of surgery and also in the recovery room followed by a mean calculation. Statistical analyses were performed by SPSS 11.0 software for Windows. Descriptive indices including frequency and mean [standard deviation (SD)] were used to express data. Continuous variables were analyzed using the Student's *t* test and paired *t* test. Nominal variables were also analyzed using the Chi-square and Fisher exact tests. P value<0.05 was considered statistically significant.

RESULTS

Mean (SD) age of experimental and control subjects was 70 (±12) and 69 (±13) years, respectively. There was no significant difference regarding age, weight, duration of surgery, and preinduction pupil diameter between the two groups ($P>0.05$) [Table 1]. The systemic blood pressure was the same between the two groups at the time of induction of anesthesia. According to blood pressures measured at 5, 10, 15, and 30 min and after the surgery, there was no difference between the two groups in hemodynamic changes during anesthesia and surgery and no difference in heart rate before and after the surgery [Table 2]. Mean (SD) recovery time (ability of patient to tell his or her name) was significantly less in the control group (19.46±5.43) than in the experimental group (33.23±10.75) ($P<0.0001$).

After induction of anesthesia, the two groups showed a significant change in pupil diameter in comparison to preinduction. The constriction effect (the difference between pre- and post-induction pupil diameter in mm) was significantly lower in experimental group (0.53±.45) compared with the control group (1.06±0.52) (P=0.0001) [Figure 1]. The percentages of constriction effect were 7.68% and 15.07% in experimental and control groups, respectively. In other words, pupil constriction was two times more intense in experimental group than in the control group after the induction of anesthesia.

DISCUSSION

Miotic action of opioids on the pupil diameter is an easily distinguishable and measurable effect in humans.[1] The neural pathways regarding pupil diameter regulations are reasonably well defined.[19] Although the exact site of action is not clear, miotic effect of opioids is probably mediated through the central nervous system.[16] In humans, opioids have a miotic effect, whereas in a number of animal studies, different mydriatic and miotic effects have been reported.[17,18-22]

Fentanyl is a potent lipid-soluble opioid and synthetic strong agonist at the μ-opioid receptors with a rapid onset and short duration of action.[25] The main functions of therapeutic value of fentanyl are analgesia and sedation.[26] The onset of action of fentanyl is almost immediate when given intravenously.[27] The usual duration of action of analgesic effect is 30–60 min after a single IV dose of up to 100 μg.[28,29]

Buprenorphine is generally described as a mixed agonist–antagonist acting mainly as a partial agonist at μ-opioid receptors, with some antagonist activity at κ receptors.[30-34] In a study in vitro, buprenorphine had slow rates of association and dissociation from the opioid receptor when compared with fentanyl.[34]

There are several published data about the effect of opioids on pupil diameter.[35-38] In one study the effect of codeine versus placebo was investigated and papillary constriction was observed after oral administration of codeine.[35] Asbury studied the effect of fentanyl and alfentanil and saline as a placebo on pupil diameter under halothane anesthesia and found that both drugs produced at least 35% reduction in mean pupil diameter compared with the placebo group.[36] This finding was similar to the finding of our study. Miller *et al.* studied the pupillary effect of morphine and alfentanil on conscious patients and allocated 40patients with American Society of Anesthesiologists grades I and II to four groups to receive either IV saline (control group), morphine 0.1 mg/kg, alfentanil 4.0 μg/kg or a combination of these doses, and pupil diameters were measured for the next 30 min.[37] There were no significant differences in the control diameters. In the opioid groups, a significant decrease in diameter (about 1 mm), occurred 4 min after administration of the drug and persisted throughout the study.

Table 1: Comparison of age, weight, duration of surgery, and preinduction pupil size between experimental and control groups

	Mean±SD		
	Experimental	Control	*P* value
Age (yr)	70.10±12.33	69.43±13.02	0.83
Weight (kg)	71.47±10.97	74.30±11.94	0.34
Preinduction pupil size (mm)	6.80±1.13	7.03±1.25	0.45
Duration of surgery	33.66 ±4.24	32.83 ±4.48	0.75

Table 2: Heart rate and blood pressure before and after the surgery

	Experimental	Control	*P* value
HR 1	80.77±15.92	80.73±15.27	0.99
HR 2	82.07±16.07	82.07±16.10	1.00
SBP 5	139.23±30.74	140.73±28.85	0.84
DBP 5	73.43±16.66	74.47±17.02	0.81
SBP 10	113.53±21.32	115.90±20.19	0.66
DBP 10	60.33±14.41	61.53±14.98	0.75
SBP15	128.20±19.87	130.9±17.27	0.57
DBP 16	72.00±16.64	71.4±14.91	0.88
SBP 30	116.23±13.63	117.07±14.62	0.82
DBP 30	65.83±13.91	65.73±13.54	0.97
SBP R	129.63±22.23	128.37±22.65	0.82
DBP R	70.33±13.77	72.40±12.72	0.54

HR1 - Heart rate in minute1; SBP 5 - Systolic blood pressure in minute 5; DBP10 - Diastolic blood pressure in minute 10; R - Recovery

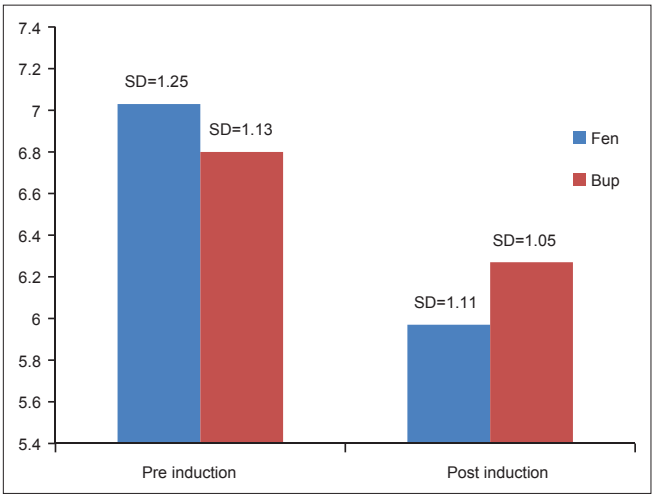

Figure 1: Comparison between the effect of fentanyl (Fen) and buprenorphine (Bup) on the pupil size in millimeters

Pickworth *et al*. performed a study regarding the effect of intravenous buprenorphine on the pupil diameter in eight nondependent male subjects who reported previous opiate use.[38] Buprenorphine (0.3, 0.6, and 1.2 mg) lessened the pupil diameter, the amplitude of the light reflex, and the speed of constriction and dilation. Significant pupillary effects occurred within 15 min of the injection and maintained for 24 h. The conclusion of that study was that the extent of the effect was not doserelated, although recovery occurred earlier after the lower dose. According to the previous studies, the pupillary measures are especially sensitive to the acute effects of full opiate agonists. The results of those studies indicated the profound and persistent effects of buprenorphine on pupillary diameter and dynamic measures.[38]

In the study conducted by Knaggs *et al*., the effects of IV morphine (0.125 mg/kg), codeine (1 mg/kg), tramadol (1.25 mg/kg), or placebo (10 mL 0.9% w/v sodium chloride) in 10 healthy patients have been assessed.[39] There was no significant change in pupil diameter after placebo. After IV morphine and codeine administration, there was a 26% decrease in pupil diameter. After administration of tramadol there were no significant changes in pupil diameter until 150 min after administration; thereafter, there was a significant reduction for the rest of the study period ($P<0.01$).

Unfortunately there is no published data that makes clear minimal acceptance pupil diameter for doing phacoemulsification (minimal risk of complication) but many surgeons believe that minimum pupil diameter for safe phacoemulsification is 5–6 mm.[40] All of our patients in experimental and control groups had pupil diameter more than 5 mm after using mydriatic drops and before surgery and unlikely to have any effect on the ophthalmologist's ability to perform cataract surgery.

CONCLUSION

According to this study, buprenorphine group had partially less pupillary constriction in comparison with fentanyl group. There was no apparent meaningful difference in other data. We strongly advocate the use of buprenorphine instead of fentanyl in patients with high risks during acataract surgery and to those with minimal response to the effect of mydriatic drops.

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