ORIGINAL ARTICLE

Safety and efficacy of fentanyl versus pethidine in cataract surgery under propofol- based sedation: A double-blind randomized controlled clinical trial

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Background: The study was aimed to evaluate the safety and efficacy of fentanyl and pethidine on the sedative quality of patients who underwent phacoemulsification cataract surgery with Propofol. **Materials and Methods:** In this double-blind randomized controlled clinical trial, patients who were candidates for elective phacoemulsification surgery with topical anesthesia were enrolled. The selected patients were randomly allocated into the two groups for receiving sedation with Propofol-Pethidine (PP) or propofol-fentanyl (PF) combinations. Demographic characteristics, hemodynamic parameters before, during, and after the operation, sedation and pain scores, and patients' and surgeons' satisfaction scores were compared in the two studied groups. **Results:** In this trial, 70 patients (35 patients in each group) have completed the study. Mean (standard deviation) operation time was 22.9 (6.8) and 25.46 (7.7) minutes in PF and PP groups ($P = 0.118$).Mean pain score in PF 0.46 (0.14) was significantly higher than PP groups 0.236 (0.06) ($P = 0.011$). The mean value of diastolic and systolic blood pressures, pulse rate, and mean arterial pressure dioxide were significantly decreased in both PF and PP groups ($P_{Time} < 0.001$), although there was no significant difference between groups. **Conclusion:** Our findings indicated the equivalence effects on hemodynamic parameters for both pethidine and fentanyl in combination with propofol in which they could provide appropriate sedation and safe anesthesia with lower complications and acceptable patients' and surgeons' satisfaction.

Key words: Cataract surgery, fentanyl, pethidine, propofol, sedation

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INTRODUCTION

Cataract is the most common cause of blindness in adults aged more than 40 years worldwide. Based on epidemiological data, it affects more than 20 million people.[1] Its surgery is also considered as the most common surgical procedure of ophthalmology practice.[2] Considering the increasing trend of life expectancy, it is assumed that the rate of cataract surgery would have an increasing trend in the world.[2,3]

Phacoemulsification is the most commonly used minimally invasive cataract surgery procedure, which has become a routine cataract extraction technique in all developed and most developing countries.[4]

In addition, considering that most of the patients are elderly cases with other concomitant diseases such as cardiovascular or respiratory disorders, they need a higher dose of analgesics.[5] Thus, appropriate pain control is considered the most important care for this group of patients.

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Although recent advances in the understanding of pain pathophysiology and pharmacology result in the development of more effective postoperative pain management techniques some patients still feel pain.[6] Recent peri and postoperative pain management protocols are focused on the control of specific pain receptors through a multimodal pharmacologic model of pain management before the effect of the painful stimulus.[7] During topical anesthesia, patients often sensing light and color, and they even see the surgeon's hands and surgery tools,[8,9] and sense pain when manipulating the iris, stretch of the globe, and inserting the lens.[10,11] Therefore, sedation or supplemental analgesia is often required during surgery.[12]

Benzodiazepines could cause some adverse effects such as prolonged efficacy, delayed patient discharge, nausea, vomiting, apnea, and muscle rigidity.[12]

Pethidine is a synthetic opioid analgesic agent of the phenylpiperidineclass. It applies its analgesic effect as a μ-opioid receptor agonist-like morphine.[13,14]

Fentanyl is a more potent opioid than pethidine. Rapidonset of action, fewer side effects, more effective sedation, and faster clearance are the superiority of fentanyl than pethidine.[15] So that, fentanyl considered a potential alternative analgesic for pethidine.

Propofol is used as an anesthetic for both inducing and maintenance of anesthesia. The most important characteristic of propofol is its short distribution half-life (2–8 min), which results in the rapid onset of anesthesia and short duration of effect. In addition, it could provide a short recovery period with less side effects.[16] As far as the authors are aware there is no study on safety and efficacy of fentanyl versus pethidine in cataract surgery under propofol-based sedation, therefore, we decided to doing the present study in patients underwent phacoemulsification cataract surgery in Isfahan, Iran.

MATERIALS AND METHODS

Study design and participation

In this double-blind randomized controlled clinical trial, patients referred to Faiz Hospital, the referral ophthalmologic hospital of Isfahan province, affiliated to Isfahan University of Medical Sciences, for elective phacoemulsification surgery were enrolled. This trial was performed form April 24, 2018 to June 22, 2019. Sample size was determined to detect the standardized effect size at least 0.7 between two competitor interventions in terms of hemodynamic parameters as main outcomes considering type one error rate 0.05, statistical power 0.8, and the same number of subjects in each group resulted 60 patients (30 patients for each group). Finally, for considering and compensating possible attrition during the study period, we recruited 35 patients in each group.

The research protocol was according to standards of the Helsinki Declaration (Edinburgh 2000) and approved by the Regional Ethics Committee of Isfahan University of Medical Sciences by number IR.MUI.REC.1396.3.854. The trial with the number IRCT20180416039326N1 was registered in the Iranian registering of clinical trials. Patients with the following:

Inclusion criteria including

- Aged 20 years old or older
- American Society of Anesthesiologists (ASA) I or II
- Informed consent to participate in the study.

Exclusion criteria including

- History of allergy to the study drugs
- Addiction to opioids or alcohol
- Psychiatric illness.

Taking any analgesic or sedative medication within 24 h before surgery.

Chronic pain syndrome,

Active upper respiratory tract infection

Asthma and chronic respiratory diseases.

Written informed consent was obtained from all selected patients after explaining the method and aims of the study.

Using a computerized random number generator, the selected patients were randomly allocated to the two groups using permuted block randomization of size 4 for underwent local anesthesia with propofol-pethidine (PP) or propofol-fentanyl (PF) combinations.

Anesthetic procedure

The anesthetic procedure was performed by an anesthesiologist who has no role in data collection. All patients in the operating room underwent pulse oximetry, capnography, electrocardiography (ECG) and automated noninvasive blood pressure monitoring.

And baseline systolic and diastolic blood pressure, mean arterial blood pressure, pulse rate, and arterial oxygen saturation were measured and recorded. The mentioned variables were measured every 5 min during surgery and every 10 min during recovery.

Before sedation induction, to prevent induction related hypotension, all patients received intravenous (IV) ringer

lactate solution with a dose of 5 ml/kg and oxygen (4 ml/min) through the nasal cannula.

The anesthesiologist, who was not involved in the data collection, 10 min before surgery, administered one drop of tetracaine 0.5% and repeat every 5 min until three doses.

Sedatives agents were prepared and injected as follows by the anesthesiologist:

- First group (F): Fentanyl 1 μg/kg, and propofol 1.0 mg/kg IV
- Second group (P): Pethidine 0.6 mg/kg and propofol 1.0 mg/kg IV.

In each group, the anesthetic agent was injected within 30 s, until reached to the proper sedation level (Ramsay score = 3), then the surgery was performed by a surgeon. In cases with inadequate sedation level, rescue dose of propofol 20 mg was injected (at a concentration of 5 mg/ml).

The level of sedation was evaluated every 5 min during surgery, hemodynamic parameters (heart rate, systolic, and diastolic blood pressure and arterial oxygen saturation) were measured and recorded by a blinded observer to the study groups, in the baseline time, during surgery every 5 min and in the recovery room every 10 min.

Any case of complication during and after the surgery was treated and documented. Desaturation (SpO_2 <92%) were treated by encouraged to breathe more, and SpO_2 <90% were ventilated with mask, and results were recorded. Patients with an Alderete score of 9 (based on modified Alderete score) discharged from the recovery. The surgeon's and patients' satisfaction scores were also evaluated and recorded after surgery and before transfer to the ward, respectively.

Sedation and pain assessment

The level of sedation in studied patients was evaluated using the Ramsay Sedation Scale by an anesthesiologist who was blinded to the study group. The scaling of the score was as follows; 1 = anxious, 2 = calm, 3 = lethargic, 4 = confuse but responding to conversation, 5 = no response to speaking, and 6 = no response to painful stimulation. Patient's ability to maintain consciousness/responsiveness during procedure considered as safe and effective level of sedation.

The pain level was assessed using a 10 scale Visual AnalogScale. The scale as follows; no pain with 0, mild pain with 1–2, moderate pain with 3–4 and 5–6, and severe pain with score > 6.

Patients' and surgeons' satisfaction

Surgeons' satisfaction score was evaluated at the end of the procedure, and patients' satisfaction score was evaluated after full recovery and/or before discharge by the trained researcher. Both tools were a 5-point Likert scale with the following scales for patients' satisfication: 0; extremely dissatisfied, 1; dissatisfied, 2; neither satisfied nor dissatisfied, 3; satisfied, 4; extremely satisfied and for surgeons' satisfication: 0; extremely poor, 1; poor, 2; fair, 3; good, 4; excellent.

Statistical analysis

Continues and categorical variables were present as mean (standard deviation [SD]) and number (%), respectively. The normal distribution of each data set was examined using Kolmogorov–Smirnov test. Independent *t*-test and Chi-square or Fisher exact tests were used for comparing basic continuous and categorical variables between studied groups repeated measures analysis of variance (ANOVA) was used for evaluating within and between-group changes in hemodynamic parameters over the study period. Mauchly's test of sphericity was conducted to assess sphericity as a perquisite assumption. Huynh-Feldt correction was adopted when this assumption was violated. When the baseline value of a hemodynamic parameter was different between two groups, it was considered a confounder, and repeated measure ANCOVA was applied. On the other hand, between groups comparisons at each time follow-up point were conducted using two independent samples *t*-test adjusted for multiple testing. $P < 0.05$ was considered as statistically significant level. All analyses were performed in SPSS (version 16, SPSS Inc., Chicago, IL, USA).

RESULTS

In this trial, as there was not any problem during the anesthetic procedure and there were not also any procedure-related complications, all initially 70 recruited patients (35 patients in each group) have completed the study [Figure 1].

Table 1 presents the basic characteristics of the study participants in two study groups. Mean (SD) age of the studied population was 66.26 (12.79). Mean age, weight, height, and body mass index of the patients in the two groups were not statistically different ($P > 0.1$). Two groups were comparable in terms of gender and ASA classification distribution ($P > 0.1$).

Table 2 depicts the mean and SD of hemodynamic parameters in two study groups before, during, and after the procedure are presented. As can be seen all hemodynamic parameters except SPO_2 showed a significant decrease in both PF and PP groups during the study course ($P_{Time} < 0.001$), although the mean values of these parameters in PF group higher than PP treated patients there was no significant difference between groups ($P_{Intervension} > 0.1$). No between

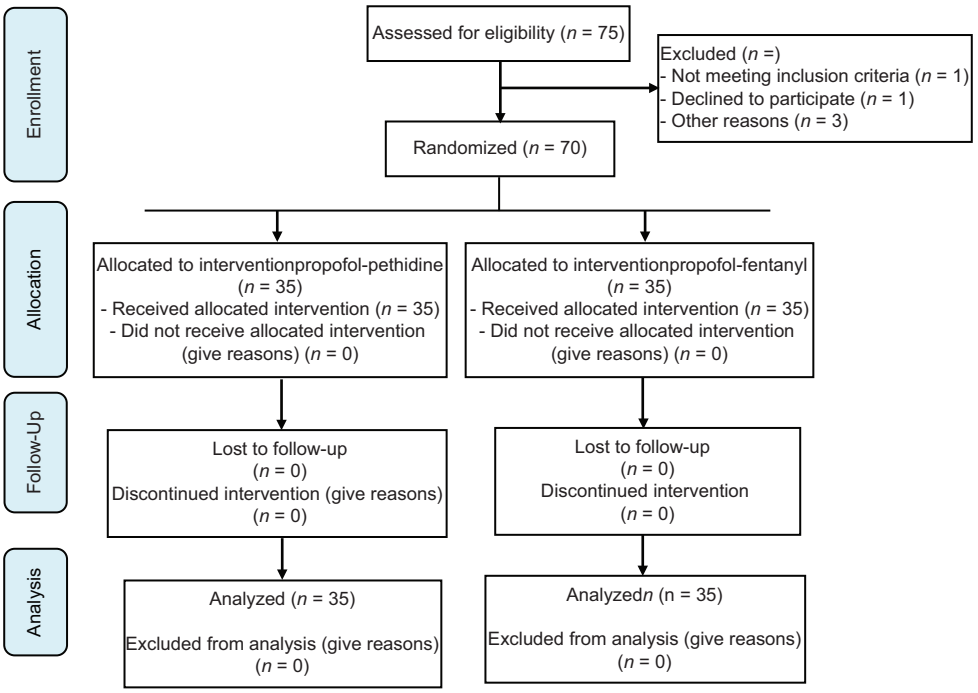

Figure 1: Consort flow diagram of patients' recruitment

Table 1: Demographic and basic characteristics of the patients in propofol-pethidine and propofol-fentanyl groups

Variables	Propofol-pethidine (*n*=35)	Propofol-fentanyl (*n*=35)	*P**
Age (years)	67.55 (14.95)	64.97 (8.74)	0.391
Sex (female/male)	18 (51.4%)/17 (48.6%)	20 (57.1%)/15 (43.9%)	0.432
ASA classification (I/II)	6 (17.6%)/29 (82.4%)	8 (22.9%)/27 (77.1%)	0.591
Weight (kg)	69.77 (15.39)	67.11 (11.65)	0.418
Height (cm)	167.88 (8.96)	166.54 (8.21)	0.519
BMI	24.58 (4.11)	24.19 (3.89)	0.657

*Resulted from independent sample *t*-test and Chi-square test for continuous and categorical data. BMI=Body mass index; ASA=American Society of Anesthesiologists

and within-group differences were observed in terms of SPO_2 in studied groups. The intervention of time was not statistically significant for none of the studied hemodynamic parameters ($P_{Time \times intervention} > 0.1$), indicating similar patterns overtime for these outcomes in two groups. Operation time was 22.9 (6.8) and 25.46 (7.7) minutes in PF and PP groups ($P = 0.118$) [Figure 2a-e].

Based on postsurgery pain assessment, mean pain score in PF 0.46 (0.144) was significantly higher than PP groups 0.236 (0.06) ($P = 0.011$). The recovery time in the fentanyl group was 24 min, and in the pethidine group was 29 min. There was no significant difference between the groups. The frequency of different levels of patients' and surgeons' satisfaction scores was comparable between the two groups. Surgeon rated his satisfaction for 26 (74.3%) as excellent, 6 patients as good (17.1%) and 3 (8.6%) as fair in PF group while he reported it in PP group as 23 (65.7%) excellent, 9 (25.7%) good and 3 (8.6%) ($P = 0.675$). Of patients in PF group 34 (97.1%) and 1 (2.9%) reported their satisfaction as excellent and good, respectively, while in PP group, all reported their satisfaction as excellent ($P = 0.501$).

In PF and PP groups for three patients and two patients, an additive dose of sedatives was administrated.

DISCUSSION

In this randomized trial study, we compared pethidine (meperidine) and fentanyl in cataract surgery under propofol-based sedation.

Both of groups provide high level of satisfaction and appropriate sedation. There was an only significant difference in pain score and postoperative diastolic and systolic blood pressure between groups. It is suggested that pethidine could provide better analgesic effect and also better control for both systolic and diastolic blood pressure.

As mentioned in order to optimize the efficacy of phacoemulsification cataract surgery and reducing the postoperative pain and some reported complications introducing of an appropriate anesthetic protocol for this procedure would be more favourable.[5-8]

In literature review we found studies which compared the efficacy of fentanyl and pethidine in combination with

Table 2: Hemodynamic parameters of patients before, during and after procedure in in propofol-pethidine and propofol-fentanyl group

Variable	Group	Time						Ptime effect	Pinteraction	Pintervention
		Before intervention	During intervention			Recovery				
PR	PF	73.41±9.80	70.15±11.98	68.53±12.21	70.26±12.38	68.35±12.27	67.15±11.43	0<0.001	0.23	0.08
	PP	79.09±18.77	79.21±17.59	75.12±15.86	74.27±16.79	73.15±16.03	70.88±15.56	0<0.001		
	P	0.27	0.04	0.12	0.45	0.3	0.27			
SBP	PF	157.03±20.26	149.17±22.20	144.46±24.29	141.06±21.74	141.06±18.59	139.74±20.02	0<0.001	0.39	0.036
	PP	144.53±20.17	143.41±18.03	138.44±17.34	135.38±18.51	133.38±16.21	129.12±15.33	0<0.001		
	P	0.01	0.28	0.28	0.30	0.07	0.01			
DBP	PF	90.40±12.33	86.66±11.71	83.74±12.98	83.54±12.28	83.11±12.49	81.89±12.57	0<0.001	0.73	0.07
	PP	85.18±11.78	82.94±11.87	81.79±11.63	79.18±14.34	77.88±12.23	75.47±12.74	0<0.001		
	P	0.08	0.21	054	0.18	0.08	0.04			
SPO2	PF	95.23±2.41	96.71±2.57	97.29±2.43	97.6±2.21	98.31±1.68	98.06±3.28	0<0.001	0.20	0.51
	PP	95.73±1.81	97.55±1.87	97.42±2.46	97.65±2.24	97.85±1.97	98.48±1.62	0<0.001		
	P	0.34	0.17	0.69	0.80	0.29	0.49			
MAP (mmHg)	PF	110.37±16.62	107.88±13.76	103.91±17.16	104.56±15.98	103.03±18.63	99.53±18.02	0<0.001	0.77	0.07
	PP	105.24±15.54	103.00±14.92	101.15±16.43	97.58±14.62	95.00±14.06	94.24±13.68	0<0.001		
	P	0.14	0.24	0.55	0.07	0.07	0.14			

P values resulted from repeated measures ANOVA and for SBP baseline value was considered as covariate and repeated measures ANCOVA was used. PP=Propofol-pethidine; PF=Propofol-fentanyl; PR=Pulse rate; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; ETCO=End-tidal carbon dioxide; ANOVA=Analysis of variance

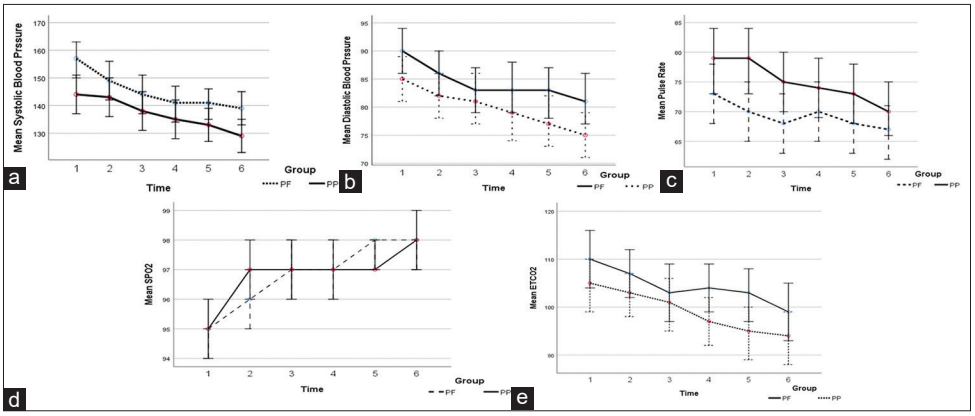

Figure 2: Mean values of (a) systolic blood pressure, (b) diastolic blood pressure, (c) pulse rate, (d) SPO_2 and (e) MAP during the study course in two study groups

other analgesic agents such as clonidine or midazolam.[17-20] In this study, we compared the efficacy of the two agents' combination with propofol.

Recently, Nishizawa and Suzuki in a review study represented the advantages of propofol use during gastrointestinal (GI) endoscopy. They concluded that due to the specific pharmacokinetic characteristics of propofol, it could be used as an appropriate sedative agent for GI endoscopy. As mentioned its properties, including excellent anesthetic effect, rapid onset of action, short half-life, and rapid recovery time, make it an excellent agent for the procedure as well as patients satisfaction. However, it has a narrow therapeutic window that could affect cardiovascular functions and patients consciousness. Hence, these potential side effects, such as cardiopulmonary complications or rapid depression of consciousness also should be considered during propofol administration during GI endoscopy.[21]

In a study in the USA, by Ali *et al*., the efficacy and safety of meperidine versus fentanyl in combination with midazolam for postprocedural pain during GI endoscopy in children was compared. They did not find any significant differences between groups regarding patients' or operator tolerance, recovery time, procedure-related complications, and hemodynamic variables. They concluded that both of the combinations had similar efficacy for analgesia during the procedure in children.[22] Our findings except for systolic and diastolic blood pressure and postoperative pain, were consistent with Alis' study.

In another study by Amornyotin *et al*. in 2013, the outcomes of deep sedation with pethidine and propofol combination were compared with moderate sedation with fentanyl and midazolam during colonoscopy in a large sample size of patients. Their findings indicated that pethidine and propofol combination had better outcome regarding

patients' and operator satisfaction and procedure-related variables such as procedure completion rate and recovery score.[23]

In a study by Fleet *et al.*, the efficacy of subcutaneous fentanyl and intranasal route with intramuscular pethidine as an analgesic for labor pain was evaluated. They demonstrated that both of them had a similar analgesic effect, whereas fentanyl provided greater satisfaction, better postlabor outcomes, and less sedation.[24] In our study, both agents provide similar satisfaction and sedation score.

Yousef *et al*. evaluate the analgesic effect of epidural fentanyl and meperidine plus clonidine in patients undergoing lower limb orthopedic surgery. Based on their findings, epidural meperidine and clonidine combination could provide more appropriate intraoperative hemodynamics outcomes and prolonged postoperative analgesic effect than epidural fentanyl and clonidine.[17] In our study, we found better hemodynamics outcomes only for blood pressure for the pethidine group.

Garda *et al*., in a retrospective study in Ireland, compared the effectiveness of pethidine and fentanyl in combination with midazolam for sedation during colonoscopy. Their results showed that patients in the fentanyl–midazolam group reported better comfort scores than pethidine-fentanyl group. They did not report any significant differences for other variables such as duration of the procedure, sedation score, and recovery time.[18]

In another study by Hayee *et al.* in the UK, compared the sedative and analgesic outcomes of midazolam-fentanyl combination versus midazolam-pethidine during colonoscopy. They reported a shorter duration of recovery but increased patients' recovery for midazolam-fentanyl combination.[19]

Robertson *et al*., in the USA, compared the outcomes of fentanyl and meperidine regarding the duration of procedure and patients discomfort during GI endoscopy. They reported that fentanyl reduce the duration of procedure due to its rapid recovery time, but meperidine has better outcome regarding postprocedure pain and patients discomfort. They concluded that a simple change in the selection of analgesic agents could improve the efficacy of procedure as well satisfaction of the patients.[25]

Study limitations were: small sample size, absence of children and pregnant women, and lack of preoperative anxiety assessment and compare it with the sedation stage.

The strength of our study was its novelty, most of the studies in this field were performed in patients underwent gastrointestinal diagnostic procedures. It was the first study that investigated the efficacy and safety of the two combinations on sedation quality during phacoemulsification cataract surgery.

Our findings indicated the equivalence effects on hemodynamic parameters for both pethidine and fentanyl in combination with propofol, in which they could provide appropriate sedation and a safe anesthesia with lower complications and acceptable patients' and surgeons' satisfaction. Further studies with a larger sample size and some other potential safe combinations are recommended.

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Conflicts of interest

There are no conflicts of interest.

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