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Research Article

Safety and Efficacy of Intravenous Sub-Dissociative Dose Ketamine vs. Sublingual Fentanyl in Cataract Surgery

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ABSTRACT

Background: Cataract surgery requires proper sedation level and immobilization of the patient. This research sought to evaluate the impact of sublingual fentanyl versus sub-dissociative dose ketamine in achieving optimal conditions in cataract surgery.
Methods: 90 participants were randomly assigned to two cohorts: sublingual fentanyl (SLF) or intravenous sub-dissociative dosage ketamine (SDK). In the SLF cohorts, fentanyl was administered sublingually at a dosage of 1.5 µg/kg and in the second cohort (SDK), ketamine was given intravenously with a dosage of 0.3 mg/kg. In both study cohorts, propofol was administered intravenously at a dosage of 0.4 mg/kg, followed by intermittent boluses of 0.1 mg/kg at 30-second intervals until desired level 4 sedation, according to the Ramsey Sedation Scale (RSS). The quality of sedation, hemodynamic parameters, patient and surgeon satisfaction, and complications were determined and compared between cohorts.
Results: No notable disparency was found among the SLF and SDK cohorts regarding the quality of sedation during the operation and recovery ($p > 0.05$). The SDK cohort demonstrated superior pain control in comparison to the SLF cohort ($p = 0.009$) and required significantly less propofol ($p = 0.047$). Hemodynamic stability, including systolic ($p<0.05$) and diastolic ($p<0.05$) blood pressure, mean arterial pressure ($p<0.05$), and heart rate ($p=0.02$), was significantly better in the SDK cohort. However, no notable disparency were observed in SpO2 levels among the two cohorts ($p>0.05$). In the SDK cohort, both patient and surgeon satisfaction were found to be greater. ($p=0.009$ and $p=0.048$, respectively). Four participants in the SLF cohort and two in the SDK cohort experienced adverse events during surgery. However, during recovery, ten participants in the SDK cohort had complications, while none of the participants in the SLF cohort exhibited adverse reactions.
Conclusion: The findings of this research suggest that SDK is a superior option for attaining optimal sedation, analgesia, and overall satisfaction for both patients and surgeons in the context of cataract surgery, particularly in comparison to SLF.

Introduction

Cataract surgery is the most commonly executed procedure conducted surgical operation involving anesthesia for individuals over the age of 50 in developed countries [1-2]. Local anesthesia and sedation are the primary modalities utilized during cataract surgery Sedative drugs should ideally not have significant side effects and ensure that patients remain hemodynamically and respiratoryly stable. Furthermore, these therapeutic agents should exhibit quick onset of effects, brief duration, non-cumulative dosage, non-toxicity, appropriate therapeutic index, and predictable

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effects. However, no single drug possesses all of these characteristics, and the selection of the pharmacological agent must be based on a thorough risk assessment and consideration of potential adverse effects [3-5]. Opioids and narcotic analgesics remain fundamental components of sedation protocols utilized worldwide [6]. fentanyl is the most frequently used opioid in the field of anesthesia, characterized by its potent μ-opioid agonist activity, rapid onset of action and minimal sedative effects [7-8]. Sublingual administration is one of several methods for using fentanyl. The analgesic effects of the sublingual route begin 5 to 10 minutes after taking a sublingual tablet [6]. The sublingual route can be particularly appealing for patients who are unable to receive opioids intravenously due to a lack of intravenous access [9].

The sublingual mucosa presents a highly favorable option for the administration of rapid-acting analgesics, owing to its rich vascularization and permeability. This route of administration holds great potential for the delivery of lipophilic opioids, such as fentanyl, due to the efficient absorption facilitated by the sublingual mucosa. Additionally, Intravenous drainage of the sublingual area is also systemic and the first effect of liver and extensive metabolism of the drug is eliminated [7].

Ketamine serves as an NMDA receptor antagonist, and when given at anesthetic doses of 1.0 mg/kg or higher via intravenous (IV) route, it exerts extensive impacts on the central nervous system, leading to a state characterized by dissociative anesthesia [10]. Ketamine has been found to be effective in sub dissociative anesthesia at doses ranging from 0.1-0.5 mg/kg, which is significantly lower than the dose required for dissociative anesthesia. Previous studies have reported the most common sub dissociative anesthesia dose of ketamine to be 0.3 mg/kg [11]. The sub-dissociative dose of ketamine provides anti-hyperalgesic, anti-allodynic, and anti-tolerance effects. Therefore, ketamine is a favorable analgesic for use in both chronic and acute pain management [12].

As far as the authors are aware, there has been no previous research conducted to evaluate the effectiveness of sub dissociative intravenous ketamine dosage and sublingual fentanyl along with propofol for sedation in cataract surgery. Therefore, the purpose of this randomized clinical trial was to evaluate the effectiveness of these two drugs s sedatives for cataract surgery.

Methods

Study design

This double-blind randomized clinical trial, followig registration in the Iranian Clinical Trial Center under ID IRCT20180416039326N18 (date: 03.08.2021), according to the Medical Declaration of Helsinki (2013), was carried out on 90 patients from March 2021 to September 2021 carried out in Faiz Ophthalmology Center in Isfahan, Iran. The ethical approval for this research was granted by the Ethics Committee of Isfahan University of Medical Sciences (IR. Mui. Med. REC.1399.103).

Patients

Inclusion and exclusion criteria: The study enrolled participants aged 50 to 75 who were deemed suitable candidates for cataract surgery utilizing phacoemulsification while under sedation. Moreover, these individuals had a physical status falling within Class I or II of the American Society of Anesthesiologists and provided consent to partake in the clinical trial. Written consent was secured from qualified participants. Patients with a history of adverse reactions to ketamine, fentanyl or propofol, pregnant women, those who had received medications other than the aforementioned drugs prior to surgery, those with unfavorable oral cavity anatomy that could interfere with sublingual drug administration, those with any kind of lesion or inflammation in the oral cavity that could interfere with sublingual drug administration, those with increased intracranial pressure, and those with a history of seizures and psychosis were not part of the study..

Exclusion criteria included a severe allergic response to any of the prescribed medicinal agents, the manifestation of significant hemodynamic disturbances, or the need for tracheal intubation or placement of a laryngeal mask during the procedure.

Randomization and Blinding

A nurse utilized a table of random numbers generated by randomization allocation software to assign patients to either the SDK or SLF group based on their time of visit. This process was continued until the desired sample size was achieved for both groups. To maintain a blinded study design, the sedation regimen administered to each participant was kept undisclosed to the patients, surgeon, and data collector.

Groups and Interventions

In the course of surgical procedures, patients received standard monitoring measures comprising ECG, pulse oximetry, non-invasive intermittent blood pressure, and capnography.

Preparation and prescription of the drugs utilized in this investigation were carried out by an anesthesiologist who had no participation in the data-gathering procedure. In accordance with the established study protocol, ketamine and propofol were administered through intravenous means, while fentanyl was administered sublingually. Oxygen was administered to patients via a nasal cannula at a flow of 4 L/min, alongside lactated Ringer's serum at a dose of 5 mL/kg. The study drugs were prepared and administered using four syringes. The first syringe was filled with fentanyl (Caspian Tamin Pharmaceutical Company) at a dose of 1.5 μg/kg up to 100 μg. The second

syringe was fill up with ketamine (PHNPHARMA GmbH, Germany) at a dosage of 0.3 mg/kg up to 20 mg. Both of these syringes were volumized with normal saline to a total volume of 2 ml. The third syringe contained 2 ml of normal saline, and all three syringes had a similar appearance. The fourth syringe, which was utilized for both study groups, was filled with propofol (Fresenius Kabi Deutschland GmbH, Germany). Ten minutes before the commencement of the procedure, in the SLF cohort, syringe number one was delivered sublingually. In the SDK cohort, syringe three was also administered sublingually. In the SLF cohort, syringe number three (saline) was intravenously injected two minutes before the procedure, whereas in the SDK cohort, syringe number two (ketamine) was intravenously injected. Moreover, to induce sedation among patients in both cohorts, syringe number four (propofol) was slowly and intravenously administered with a dosage of 0.4 mg/kg. Boluses of 0.1 mg/kg were then intermittently delivered every 30 seconds until the preferred degree of sedation was attained. Throughout the procedure, additional bolus doses of 0.1 mg/kg propofol were administered at 30-second intervals, if required, to sustain the optimal level of sedation [13].

Outcome measures

The principal aims of the research were to compare the effectiveness of sedation and pain alleviation in the two cohorts throughout surgery. Secondary outcomes included evaluating adverse effects, the demand for supplementary sedation, and variation in hemodynamic indicators.

The depth of sedation was assessed utilizing the Ramsay Sedation score, with the objective of achieving a sedation score between 3 and 4 on the scale. This scale ranges from 0 to 6, with 0 denoting a state of wakefulness and orientation, 1 representing anxiousness, agitation, or restlessness, 2 indicating cooperation, orientation, and tranquility, 3 signifying responsiveness solely to commands, 4 denoting a state of slumber with a prompt reaction to stimuli, 5 representing a sluggish response to stimuli, and 6 indicating an absence of response to stimuli [14]. In case of anxiety of the patient during surgery and the need for deeper sedation, a rescue dose of 2 ml of propofol with a concentration of 5 mg/ml was prescribed and recorded.

The assessment of the patient's pain intensity was conducted at regular intervals during the postoperative recovery phase, occurring every 15 minutes. Similarly, the first half hour of transfer to the ward was also monitored using a 10-point visual analog scale (VAS), which comprises the range of 0 (indicative of no pain) to 10 (indicative of the highest level of pain imaginable) [15]. If a VAS score exceeded 2, Apotel at a dosage of 15 mg/kg was administered to both groups. Subsequently, both patient and surgeon satisfaction were evaluated with the application of a 5-point Likert scale. To investigate the occurrence of adverse effects such as hypertension, hypotension, tachycardia, bradycardia, nausea, and vomiting, as well as hallucinations, various methods were employed. Vital signs were closely monitored, and the patient was observed and questioned in relation to the particular type of complication.

Statistical Analysis

The data acquired were ultimately inputted into SPSS software version 26, created by IBM Corp. in Armonk, N.Y., USA. Variables possessing quantitative characteristics were manifested through mean± standard deviation (SD), while those with qualitative characteristics were expressed through frequency and percentages. For statistical analysis, the t-test was employed to examine the between-cohort differences in age, BMI, average level of sedation, pain intensity, and changes in hemodynamic parameters. To assess the between-cohort differences in gender and ASA status, frequency of pain, and adverse effects the $\chi 2$ test or Fisher Exact test was utilized. A 5% alpha error (95% confidence interval) was employed as the threshold for accepting or rejecting the null hypothesis. In this study, P value < 0.05 was considered statistically notable.

Results

A total of 90 individuals were participated, but three patients were excluded from the final analysis. Hence, the SDK cohort comprised 42 patients, whereas the SLF cohort included 45 patients (Figure 1).

The findings manifested that the average age of individuals in the fentanyl cohort was 58.07 ± 10.16 years, in contrast to 62.15 ± 11.75 years for those in the ketamine cohort. Furthermore, the proportion of female patients was recorded at 44.4% in the fentanyl cohort and 52.4% in the ketamine cohort. Statistical evaluations confirmed that the demographic attributes, including age, weight, height, Body Mass Index, and gender, were uniform across both cohorts. ($p > 0.05$) (Table 1). No significant disparency was observed in RSS (sedation score) at various time points during surgery and recovery among the two cohorts ($p>0.05$). While there was no notable difference in the Visual Analog Scale (VAS) scores between the two cohorts at the initial recovery phase, the SLF cohort demonstrated an increased pain score at the final recovery assessment ($p=0.009$). The length of sedation experienced by the SDK cohort was markedly greater than that of the SLF cohort ($p=0.003$). In contrast, the amount of propofol given to the SLF cohort was considerably higher compared to the SDK cohort ($p < 0.047$). Nevertheless, no significant difference was observed in the recovery duration between the SLF and SDK cohorts. ($p > 0.541$) (Table 2). Concerning hemodynamic indicators like systolic and

diastolic blood pressure, mean arterial pressure, and heart rate, the SDK cohort exhibited significantly greater stability throughout the different phases of surgery and recovery ($p<0.05$). In contrast, no difference significances were observed between the SLF and SDK cohorts regarding SpO2 levels. ($P > 0.05$) (Table 3). Surgeons indicated greater satisfaction levels among patients who were administered ketamine as opposed to those who were given fentanyl. ($p < 0.04$). Furthermore, Patient administered ketamine exhibited higher levels of satisfaction in contrast to those who were given fentanyl (Figure 2).

In the course of the surgical procedures, two individuals within the SDK cohort exhibited symptoms of hypertension and tachycardia. In contrast four patients in the SLF cohort exhibited hypotension and hypertension. Notably, there were no reported complications during the recovery phase for patients in the SLF cohort, whereas ten patients from the SDK cohort encountered complications, with nausea identified as the predominant issue (Table 4).

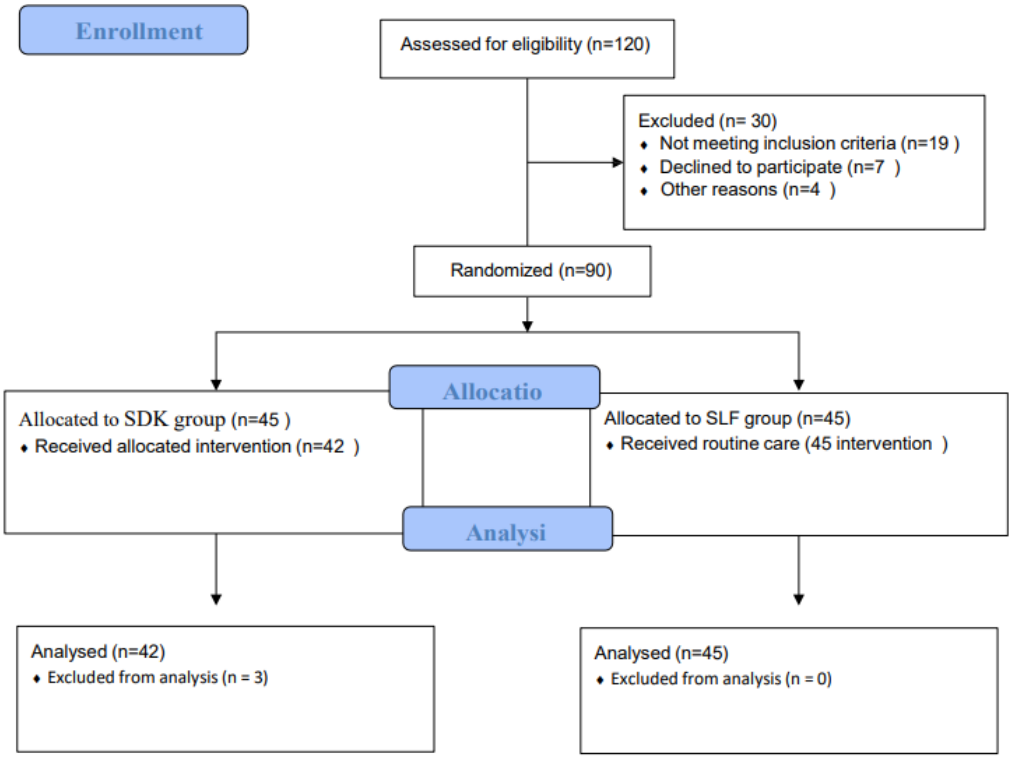

Figure 1- Consort diagram of study.

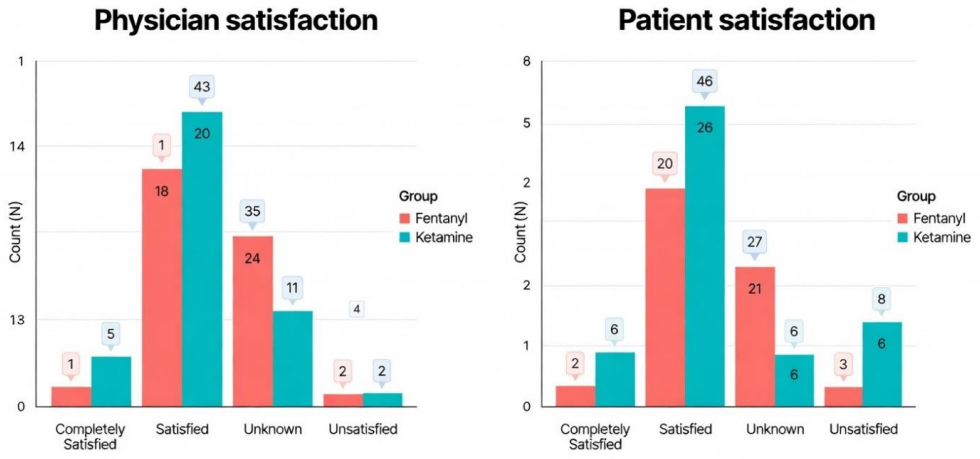

Figure 2- Satisfaction percentage of patients and surgeons.

Table 1- Baseline attributes of participants.

Quantitative variable		Group	Mean (SD)	P value*
Age		SLF	58.07 (10.16)	0.088
		SDK	62.15 (11.75)	
Weight		SLF	72.75 (12.45)	0.304
		SDK	75.81 (14.95)	
Height		SLF	163.53 (8.53)	0.627
		SDK	162 (19.16)	
BMI		SLF	27.10 (3.41)	0.211
		SDK	32.68 (29.52)	
Qualitative variable		Group (N (%))		P value**
		SLF	SDK	
Gender	Female	20 (44.4%)	22 (52.4%)	0.459
	Male	25 (55.6%)	20 (47.6%)	
ASA	1	7 (15.6%)	14 (34.1%)	0.103
	2	38 (84.4%)	27 (65.9%)	

Data are expressed as mean ± standard deviation or number (%). *: Independence t-test. **: Chi-Square. ASA, American Society of Anesthesiologists, physical status classification.

Table 2- Comparison of quality of sedation and pain control, duration of sedation, recovery stay, and propofol usage

		Median [IQR]		P value*
		SLF	SDK	
RSS	Operation (every 5 minutes)	1 [1]	1 [1]	0.483
		1 [1]	1 [1]	0.689
	Recovery (every 15 minutes)	1 [1]	1 [1]	0.311
		1 [1]	1 [1]	0.136
VAS	Recovery (every 15 minutes)	1 [1]	1 [1]	0.190
		1 [1]	1 [2]	0.009
Sedation duration		20 [10]	20 [0]	0.003
Length of stay in recovery		30 [0]	30 [0]	0.541
Propofol dose		2 [1]	2 [1]	0.047
Propofol frequency		Group (N, %)		0.446**
		1 14 (33.3%)	15 (44.1%)	
		2 20 (47.6%)	16 (74.1%)	
		3 7 (16.7%)	3 (8.8%)	
		4 1 (2.4%)	0	

* Mann-Whitney U. **likelihood ratio test. RSS, Ramsay sedation scale.

Table 3- Hemodynamic parameters

Variable	Time	Group		P value[a]
		SLF (Mean (SD))	SDK (Mean (SD))	
SBP	Before	133.07 (25.42)	146.1 (20.40)	0.010
	During operation every 5 minutes	130.56 (29.30)	137.93 (15.81)	0.145
		127.82 (21.17)	140.74 (19.07)	0.004
	Recovery every 15 minutes	130.73 (23.78)	144.45 (20.81)	0.005
		128.84 (19.62)	145.66 (22.28)	<0.001
DBP	Before	84.53 (14.71)	89.79 (12.37)	0.076
	During operation every 5 minutes	82.67 (12.26)	85.6 (11.74)	0.259
		79.07 (11.13)	85.26 (11.27)	0.012
	Recovery every 15 minutes	80.60 (13.26)	89.26 (12.85)	0.003
		83.8 (17.24)	87.85 (13.38)	0.230
MAP	Before	101.93 (17.81)	112.07 (15.58)	0.006
	During operation every 5 minutes	101.51 (16.17)	104.79 (13.88)	0.315
		96.91 (15.03)	107.64 (18.03)	0.003
	Recovery every 15 minutes	99.67 (17.09)	110.17 (17.61)	0.006
		101.27 (15.78)	110.39 (17.05)	0.012

HR	Before	73.89 (13.48)	79.55 (13.89)	0.057
	During operation every 5 minutes	72.98 (13.19)	77.52 (15.20)	0.139
		70.78 (13.09)	76.02 (12.77)	0.062
	Recovery every 15 minutes	69.02 (12.78)	74.62 (10.45)	0.029
		70.69 (17.41)	74.15 (12.90)	0.302
Variable	Time	Median [IQR]		P value[b]
SpO_2	Before	98 [2]	97 [2]	0.619
	During operation every 5 minutes	97 [1]	98 [2]	0.847
		98 [1]	98 [2]	0.136
	Recovery every 15 minutes	98 [1]	98 [2]	0.508
		98 [1]	98 [1]	0.292

a= Parametric test (t-test) - for normally distributed data (presented as Mean±SD)

b= Non-parametric test (Mann-Whitney U) - for non-normally distributed data (presented as Median [IQR])

Table 4- Adverse effects

Time	Adverse effects	Group	
		SDK (n=42)	SLF (n=45)
During surgery	Hypotension	0(0)	2 (4.4)
	Hypertension	1 (2.38)	2 (4.4)
	Tachycardia	1 (2.38)	0
	None	41 (95.24)	41 (91.2)
During recovery	Nausea	5 (11.9)	0
	Vomiting	1 (2.38)	0
	Hallucination	2 (4.76)	0
	Nausea and vomiting	2 (4.76)	0
	None	32 (76.16)	45 (100)

Discussion

This investigation examined the impact of intravenous administration of a Sub-dissociative dose of ketamine compared to sublingual administration of fentanyl on sedation quality, analgesia and hemodynamic parameters in cataract surgery. The preliminary findings of this inquiry indicate that there were no notable discrepancies between the two study cohorts regarding demographic factors, such as age, gender, body mass index, and ASA. Therefore, it is likely that the observed distinctions between the two cohorts were associated with the type of analgesic employed.

This research indicated that the sedation quality (RSS) was comparable in both cohorts throughout the study duration. It is important to emphasize that the SLF cohort was given a higher dose of propofol to achieve similar sedation levels as the SDK cohort. Nevertheless, there was no notable difference between the two cohorts regarding the duration of recovery stay. In addition, the SDK cohort showed better pain control in recovery compared to the SLF cohort.

The changes noted in hemodynamic parameters and Spo2 percentage during surgery and recovery did not notable differences between the two cohorts. The SDK cohort demonstrated a greater degree of satisfaction among both patients and surgeons. In alignment with the current investigation, a meta-analysis conducted by Lee et al. demonstrated the potential effectiveness of low-dose ketamine as an agent for alleviating pain in the emergency department [16]. Similarly, Motov et al. conducted a study in which sub-dissociative low-dose ketamine utilized for addressing both acute and chronic pain conditions within the emergency department. Their findings indicated that, in the context of painful conditions, low-dose ketamine use correlated with a reduction in the overall demand for analgesics and opioids [17]. Hashemi et al. conducted a study involving patients aged 18 years or younger who suffered from cancer pain. Sublingual fentanyl was administered in doses of 100 µg and 200 µg to facilitate pain relief. The findings of the research demonstrated that sublingual fentanyl exhibits efficacy in terms of rapid-onset pain relief with a brief duration of action, and is considered a safe and tolerable treatment option. Thus, this treatment modality is deemed appropriate for patients who experience episodes of pain related to cancer [12], the findings of the current research align with those of Hashemi's study regarding the analgesic properties of sublingual fentanyl.

The findings of Motov's investigation indicated that patients with limb fractures who were treated with nebulized fentanyl experienced a notably elevated level of pain in comparison to those administered with 0.4 mg/kg ketamine intravenously [17]. In the present investigation, the SDK cohort exhibited superior effectiveness in pain management throughout the recovery phase, aligning with the findings of Motov's

research. It should be noted that, in our study, the sublingual fentanyl was used, while the nebulizer fentanyl was used in the above study.

"In the research of Khajavi et al., on colonoscopy under sedation, the first cohort received fentanyl (1 µg/kg), whereas the second cohort received ketamine (0.5 mg/kg). Propofol (0.5 mg/kg) was administered to both cohorts. The results showed that the level of sedation was similar in both cohorts [18].

Messenger et al. performed a research in the emergency department, wherein either ketamine at a dosage of 0.3 mg/kg or fentanyl at a dosage of 1.5 µg/kg were administered intravenously, following which propofol was titrated intravenously to achieve deep sedation. The researchers concluded that a low dose of ketamine may have comparable efficacy to fentanyl in achieving the desired level of sedation [13].

Frey et al. in a study concluded that intranasal ketamine 1.5 mg/kg provides adequate pain relief, which is less than fentanyl 2.0 µg/kg, and intranasal ketamine could be a suitable substitute to intranasal fentanyl in managing pain related acute organ damage [19].

In a study by Forghani et al., fentanyl 1 µg/kg and ketamine 0.3 mg/kg were associated with a reduction in limb fracture pain in patients taking methadone [20].

In the current study, SDK showed more efficacy than fentanyl (sublingual) in relieving pain, which is consistent with previous studies [3,7].

In research carried out by Poolsuppasit et al., it was found that administering low-dose ketamine in conjunction with propofol for individuals undergoing uterine curettage results in reduced instances of hypotension compared to the use of fentanyl in combination with propofol. [21]. Hasanein and his team employed combinations of ketamine-propofol and fentanyl-propofol as sedative agents for obese individuals undergoing the endoscopic retrograde cholangiopancreatography (ERCP) procedure. In the first cohort, a dosage of 2 ml of ketamine (50 mg/ml) was utilized, while in the second cohort, fentanyl was driven at a rate of 1.5 µg/kg. In both cohorts, 40 ml of 1% propofol (10 mg/ml) was infused to achieve sedation. The researchers reported that the total volume of propofol utilized in the fentanyl-propofol cohort was notably higher in comparison to the ketamine-propofol cohort [22]. The results of the current investigation indicate that the requirement for propofol in the sublingual fentanyl cohort surpasses that of intravenous ketamine, which is consistent with the outcomes of Hasanein's research. A separate investigation was carried out to evaluate the efficacy of Propofol-Ketamine (PK) versus Propofol-Fentanyl (PF) combinations in patients receiving closed reduction procedures in emergency departments. The results revealed that the level of patient satisfaction was notably elevated among those in the PK cohort [23]. Heidari et al compared propofol-ketamine and propofol-fentanyl in cataract surgery sedation, discovering no notable disparency in satisfaction levels among patients and surgeons [24]. Similarly, in the current study, Surgeon and patient satisfaction were also significantly higher in the SDK cohort, which aligns with the aforementioned study. The present research presents certain limitations that need to be acknowledged. Initially, the survey was conducted on a limited cohort of participants who had undergone cataract surgery. People with ASA class higher than 2 were not entered in the research. In addition, the assessment of sedation levels lacked objective measurements that could affect the accuracy of the findings.

Conclusion

The results of this research signify that sub-dissociative intravenous ketamine is a more effective choice for achieving optimal sedation, analgesia, and satisfaction for both patients and surgeons during cataract surgery when compared to sublingual fentanyl.

What is known

- Cataract surgery requires adequate sedation, analgesia, and patient immobilization to ensure optimal surgical conditions.
- Both fentanyl and ketamine are potential agents that are frequently used in the field of anesthesia.

What is new

- The SDK demonstrated greater pain control and less propofol usage compared to SLF.
- The SDK resulted in better hemodynamic stability and higher patient and surgeon satisfaction than SLF.

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Ethics approval and consent to participate

The ethics committee of Isfahan University of Medical Sciences granted approval for the study protocol. provided informed consent prior to participation. The study adhered to relevant guidelines and regulations, including the Declaration of Helsinki.

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Authors' contributions

HS and LA designed the study, NNE collected the data, HS and NNE drafted and revised the final edition of manuscript.

Data availability

Data associated with this article are accessible from the corresponding author upon a moderate request.

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