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Research Paper

Comparing the Effects of Lidocaine/Paracetamol and Midazolam/Fentanyl as a Premedication on Pain Intensity and Hemodynamic Changes in Patients Undergoing Cataract Surgery With Topical Anesthesia: A Randomized Double-blinded Pilot Study

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ABSTRACT

Background: Several supplementary approaches have been used to increase the patient's comfort during phacoemulsification under topical anesthesia.

Objective: This study aimed to compare the effects of lidocaine/paracetamol (LP) and midazolam/fentanyl (MF) administration on pain intensity and hemodynamic changes in patients undergoing cataract surgery using phacoemulsification.

Methods: This study was designed and implemented as a pilot randomized double-blinded clinical trial. A total number of 80 patients with cataracts scheduled for phacoemulsification were randomly assigned to two groups (40 subjects in each group) to receive lidocaine at a dose of 1.5 mg/kg and then infused with 1 g of paracetamol in 100 cc of normal saline (LP group) or midazolam 0.2 mg/kg and fentanyl 1.5 µg/kg (MF group). Hemodynamic parameters and sedation scores were measured before, 5, and 15 minutes after surgery, and then during recovery. Furthermore, pain (VAS), patient-surgeon satisfaction, propofol, and opioid consumption were all assessed.

Findings: The sedation scores during recovery in the LP group were significantly lower (P= 0.04) than those in the MF group. Respiratory depression was also significantly lower (P<0.001) in the LP group compared to that infused by MF. According to other findings, no significant difference was observed between both study groups.

Conclusion: The use of lidocaine-paracetamol as a supplementary approach for patients undergoing cataract surgery under topical anesthesia can cause better sedation scores with lower respiratory depression compared to the use of midazolam-fentanyl.

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1. Introduction

Nowadays, most cataract surgeries are performed by phacoemulsification under topical anesthesia. Topical anesthesia preserves patients from globe injuries, optic nerve damage, and respiratory problems [1, 2]. Topical anesthesia has further benefits, such as immediate visual improvement, absence of interference with visual function, lack of injection-related pain, and unlimited ocular motility without an increase in orbital volume [1, 3].

Several drugs, such as propofol, benzodiazepine, opioids, melatonin, and dexmedetomidine, have been employed for sedation during this procedure. However, these drugs may cause over-sedation, disorientation, reduction of cognitive functioning, respiratory depression, bradycardia, and cardiovascular depression [3].

However, each of these agents has its limitations, leading to disturbance of respiratory and circulatory function, and impaired patient cooperation during surgery, and thereby these methods work less than ideal agents for the management of conscious sedation. Therefore, the potential clinical advantages of new drug combinations in this setting still need to be evaluated.

Previous studies have revealed that paracetamol is an effective analgesic in approximately half of the patients with acute pain within 4 h of surgery [4]. Moreover, paracetamol easily crosses the blood brain barrier (BBB) and in vivo effects of paracetamol are similar to those of the selective cyclooxygenase-2 (COX-2) inhibitors [5]. On the other hand, Connolly KP et al. declared that the inclusion of IV acetaminophen as part of a multimodal pain regimen led to fewer episodes of delirium in geriatric patients. Reduced use of opioid after surgery may be a crucial factor in this outcome. Low rates of delirium may reduce hospitalization and hospital costs [6].

Also, lidocaine is a short-acting amide local anesthetic that has analgesic, anti-inflammatory, and anti-hypertensive properties. Furthermore, it has been reported that intra-peritoneal and intravenous use of lidocaine, especially for abdominal surgeries, causes an early return of bowel movements and also reduces postoperative nausea and vomiting, the need for analgesia, and the length of hospital stay [7]. According to the review of the related literature and according to the author's knowledge, no study has been conducted so far in the form of a double-blinded clinical trial comparing the effects of lidocaine/paracetamol (LP) and midazolam/fentanyl (MF); however, some studies were conducted to examine the controversial conclusions on the effects of paracetamol in cataract surgery. A synergistic effect of two agents reduces the dose for both agents and therefore reduces the side effects by improving efficacy.

Therefore, the present study was conducted to compare the effects of LP and MF administration on pain and hemodynamic changes in patients undergoing cataract surgery using a topical anesthetic technique.

2. Material and Methods

This study was designed and implemented in the form of a randomized double-blinded parallel clinical trial. The study was approved by the institutional Ethics Committee. Patients were fully informed about the study protocol and gave informed consent. The study was conducted on 80 patients who were scheduled for phacoemulsification cataract surgery aged 50-80 years with American society of anesthesiologists (ASA) physical status I-III at the Velayate Hospital, which is an ophthalmic center affiliated with the Qazvin University of Medical Sciences in Qazvin City, Iran in June 2019 to September 2019. The exclusion criteria included the history of seizure, allergies to any of the drugs used in the study, hypertension, mental or neurological diseases, history of chronic consumption of non-steroidal anti-inflammatory drugs (NSAIDs), addiction, as well as the patient's unwillingness to answer research questions.

Randomization was based on computer-generated codes. Allocation was achieved by a resident outside of the project, and the study drugs were given by a nurse not involved in the study. The nurse was not blinded but was not involved in the study. The anesthetist was blinded to the patient's group assignment, and the study data was recorded by a blinded observer.

During phacoemulsification, the patients received the bolus administration of intravenous lidocaine at a dose of 1.5 mg/kg and an infusion of 1 g paracetamol in 100 mL of normal saline (LP group) or bolus administration of intravenous midazolam at a dose of 0.02 mg/kg and fentanyl at a dose of 1.5 mg/kg (MF group).

No premedication was given except for the drugs programmed by the study protocol. In case of restlessness during surgery (sedation score <2), propofol was injected with a titration dose of 10 mg. The amount of propofol in patients was also recorded in a questionnaire for each patient. Moreover, the ophthalmologist, who was uninformed of the patient's assignment, applied

the topical anesthesia by the instillation of two drops of 0.5% tetracaine in the lower fornix 5 minutes before surgery. The lids and periocular areas were stained twice with 5% povidone-iodine solution, and the patient was draped. While fully draped, the eye speculum was inserted, and immediately after, 0.1 mL of the solution (2.5 mL 2% lidocaine, 0.5 mL 1/10000 epinephrine, and 2 mL of balanced salt solution) prepared by a nurse, was generously poured on the exposed ocular surface. The entry into the anterior chamber was followed by an intracameral injection of 0.1 mL of the solution mentioned above. Phacoemulsification was performed by the Stop and Chop technique with the Baush and Lamb Stellaris device. The cornea was completely sealed using stromal hydration without sutures.

Hemodynamic parameters were assessed before drug injection (T1), 5 minutes after drug injection (T2), 10 minutes after drug injection (T3), 5 minutes after surgery (T4), 10 minutes after the start of surgery (T5), and postoperatively before discharge from the recovery room (T6). The sedation level of patients after surgery was assessed according to the modified Ramsay score scale [8], using a 3-point scale with 1=anxious, 2=calm and oriented and, 3=calm and drowsiness. Complications, such as respiratory depression, headaches, nausea, vomiting, and chills, were also recorded. Patients were preoperatively elucidated to use a visual analog scale (VAS) of pain from 0 to 10 (0 no pain, 10 maximums imaginable pain) to assess pain. The patient's pain was assessed immediately after surgery and 30 minutes after the patient entered the recovery room using the visual analogue scale (VAS).

Postoperatively, the surgeon, who was unaware of the patient assignment, was asked to assess the adequacy of intraoperative conditions according to the following scale, including excellent (complete calmness and cooperating with the surgeon), good (slight undesirable movements of the eye, and poor (severe undesirable movements of the eye and un-cooperating) as well as, patient satisfaction was assessed by the Iowa satisfaction with anesthesia scale (ISAS) [9] as a standardized questionnaire and its results were compared among all subjects.

Statistical analysis

To calculate the sample size, data from previous similar studies were considered. [3] Sample size analysis determined that a total of 60 patients per group were required to detect a 20-minute difference in the mean duration of analgesia between the groups using the Mann–Whitney U test, with a power of 0.9 and α equal to 0.05. We assigned 40 patients to each group to allow for dropouts and protocol violations. Parametric data were expressed as the Mean±SD. The normality of the data was tested using a one-sample Kolmogorov–Smirnov test. The t-test analysis was used for continuous parametric variables. Nonparametric data were expressed as the median interquartile range. The pain scores and patient satisfaction in both groups were correspondingly compared via Fisher's exact test or Chi-square test in case of normal distribution of the data; otherwise, the Mann-Whitney U test was employed. Inter- and intra-group tests were also performed using t-test and repeated measures analysis, respectively. A $P<0.05$ was considered significant. Statistical analysis was performed using SPSS software, version 16 (SPSS, Chicago, IL).

3. Results

Among the 86 patients initially enrolled in this study, 6 cases were excluded due to protocol limitations or other violations of the study protocol. Eighty patients were randomly assigned to two groups (Figure 1).

As shown in Table 1, no significant differences were observed between the two groups regarding the demographic features, including age and American society of anesthesiologists (ASA) classification, except for gender.

No significant difference was also observed between both groups in terms of pain scores at different times (P=0.586). Regarding sedation scores, a significant difference was observed between both study groups after surgery. During surgery in the LP group, 26 patients were very calm and 14 of them were calm but 16 patients receiving MF were very calm, 22 of them were calm, and the 2 others were slightly restless, with a statistically significant difference (P=0.046) (Table 2).

The surgeon reported a similar quality of operating conditions during surgery in the LP group. As a whole, no significant difference was observed between both groups in terms of surgeon-patient satisfaction.

The difference in the relative frequency of patients who received propofol in MF 13 (32.5%) and in LP 10 (25%) groups was not statistically significant (P=0.622). In other words, no significant difference was observed in the need for additional propofol (mg) between the patients in the MF (7.25±12.4) and LP (5.00±9.6) groups (P=0.433).

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Table 1. Comparing demographic data of patients in Lidocaine/Paracetamol (LP) and Midazolam/Fentanyl (MF) Groups[a]

Variables		No. (%) (n=40)		P[b]
		LP	MF	
Gender	Male	19(47.5)	30(75)	0.021
	Female	21(52.5)	10(25)	
ASA	I	13(32.5)	10(25)	0.459
	II	27(67.5)	30(75)	
Age	40-50	2(5)	6(15)	0.450
	51-60	15(37.5)	12(30)	
	61-70	9(22.5)	8(20)	
	71-80	5(12.5)	8(20)	
	81-90	9(22.5)	6(15)	

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Abbreviations: MF: Midazolam-fentanyl; LP: Lidocaine-paracetamol; ASA: American society of anesthesiologists.[a]. All values are presented as No. (%). [b] Pearson Chi-Square was used for nonparametric data and t-test was used for parametric data.

Table 2. Comparing sedation scores of patients during surgery in Lidocaine/Paracetamol (LP) and Midazolam/Fentanyl (MF) groups

Sedation Scores	Group	No. (%), (n=40)		P[c]
		MF	LP	
During Surgery	Very calm	16(40)	26(65)	0.046
	Calm	22(55)	14(35)	
	Restless	2(5)	0(0)	

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Abbreviations: MF: Midazolam-fentanyl; LP: Lidocaine-paracetamol. [c] Pearson Chi-Square test.

Table 3. Distribution of Mean±SD of heart rate in Lidocaine/Paracetamol (LP) and Midazolam/Fentanyl (MF) groups

Time		Before Drug Injection (T1)	Five Minutes After Drug Injection (T2)	Ten Minutes After Drug Injection (T3)	Five Minutes After the Start of Surgery (T4)	Ten Minutes After the Start of Surgery (T5)	Postoperatively Before Discharge From the Recovery Room (T6)
Group heart rate Mean±SD	LP	75.88±15.36	76.73±13.30	73.93±16.56	76.10±12.54	76.18±12.79	75.18±13.07
	MF	70.63±15.63	70.88±15.29	71.03±14.96	71.35±14.09	73.55±12.72	72.08±12.76
The result of ANOVA for repeated measures	Time effect			F=1.465	(P=0.225)	Partial eta2=0.018	
	Group effect			F=1.926	(P=0.169)	Partial eta2=0.024	
	Group–by–time Interaction effect			F=1.140	(P=0.333)	Partial eta2=0.014	

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Abbreviations: MF: Mmidazolam-fentanyl; LP: Lidocaine-paracetamol; ANOVA: Analysis of variance. Values are expressed as Mean±SD. P are from independent samples t-test.

Table 4. Distribution of Mean±SD of meanarterial pressure in Lidocaine/Paracetamol (LP) and Midazolam/Fentanyl (MF) groups

Time		Before Drug Injection (T1)	Five Minutes After Drug Injection (T2)	Ten Minutes After Drug Injection (T3)	Five Minutes After the Start of Surgery (T4)	Ten Minutes After the Start of Surgery (T5)	Postoperatively Before Discharge From the Recovery Room (T6)
Group mean arterial pressure Mean±SD	LP	106/85±14.73	104.03±13.49	105.58±13.62	104.70±13.40	103.30±14.77	100.48±14.62
	MF	108.45±17.68	104.65±13.74	103.78±15.57	103.05±15.7	103.30±15.73	101.60±15.60
The result of ANOVA for repeated measures	Time effect			F=6.776	(P<0.001)	Partial eta2=0.080	
	Group effect			F<0.001	(P=0.994)	Partial eta2<0.001	
	Group – by – time interaction effect			F=0.749	(P=0.505)	Partial eta2=0.010	

Abbreviations: MF: Midazolam-fentanyl; LP: Lidocaine-paracetamol; ANOVA: Analysis of variance. Values are expressed as Mean±SD. P are from independent samples t-test.

As shown in Figure 2, Table 3, and Table 4, no significant difference was observed in hemodynamic parameters between the two groups in terms of heart rate (P=0.338) and mean arterial pressure (P=0.587).

Table 5 and Figure 3 show a significant difference in the respiratory rate at various time points between the two groups. The repeated measures analysis showed that the difference in change in the respiratory rate at various time points between the two groups was significant (P=0.002).

In the MF group, respiratory rate depression was followed by drug injection, which was significantly higher than in the LP group.

4. Discussion

Table 5. Distribution of Mean±SD respiratory rate in Lidocaine/Paracetamol (LP) and Midazolam/Fentanyl (MF) groups

Time		Before Drug Injection (T1)	Five Minutes After Drug Injection (T2)	Ten Minutes After Drug Injection (T3)	Five Minutes After the Start of Surgery (T4)	Ten Minutes After the Start of Surgery (T5)	Postoperatively Before Discharge From the Recovery Room (T6)
Group respiratory rate Mean±SD	LP	15.5±1.76	14.98±1.47	15.05±1.72	15.33±1.89	15.03±1.57	14.65±1.80
	MF	17±2.33	11.78±1.60	12.40±1.89	12.85±1.86	13.85±1.80	13.58±1.58
The result of ANOVA for repeated measures	Time effect			F=41.151	(P<0.001)	Partial eta2=0.345	
	Group effect			F=29.346	(P<0.001)	Partial eta2=0.273	
	Group–by–time Interaction effect			F=29.248	(P=0.001)	Partial eta2=0.273	

Abbreviations: MF: Midazolam-fentanyl; LP: Lidocaine-paracetamol; ANOVA: Analysis of variance. Values are expressed as mean (standard deviation). P are from independent samples t-test.

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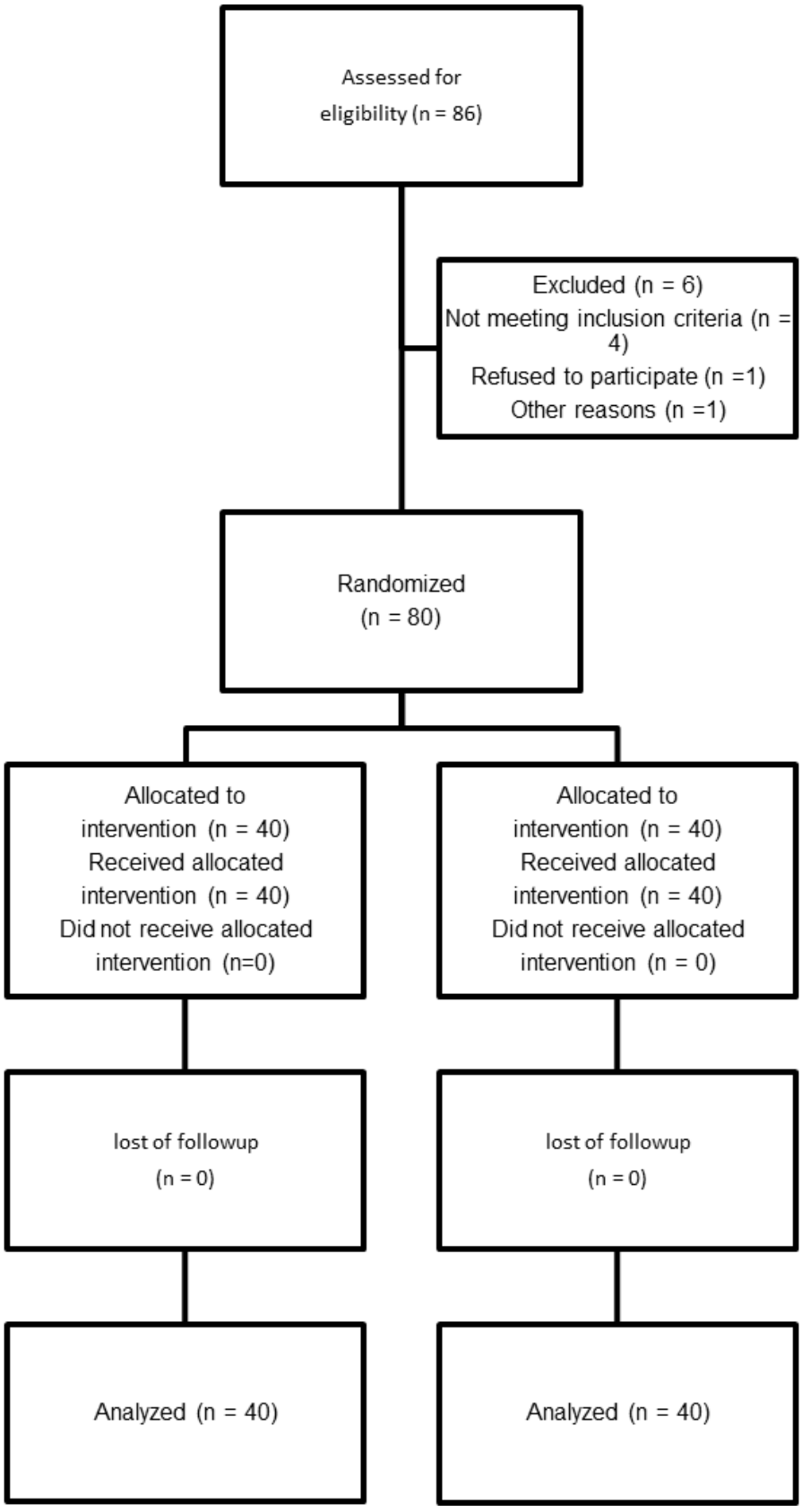

Figure 1. Consort flow diagram

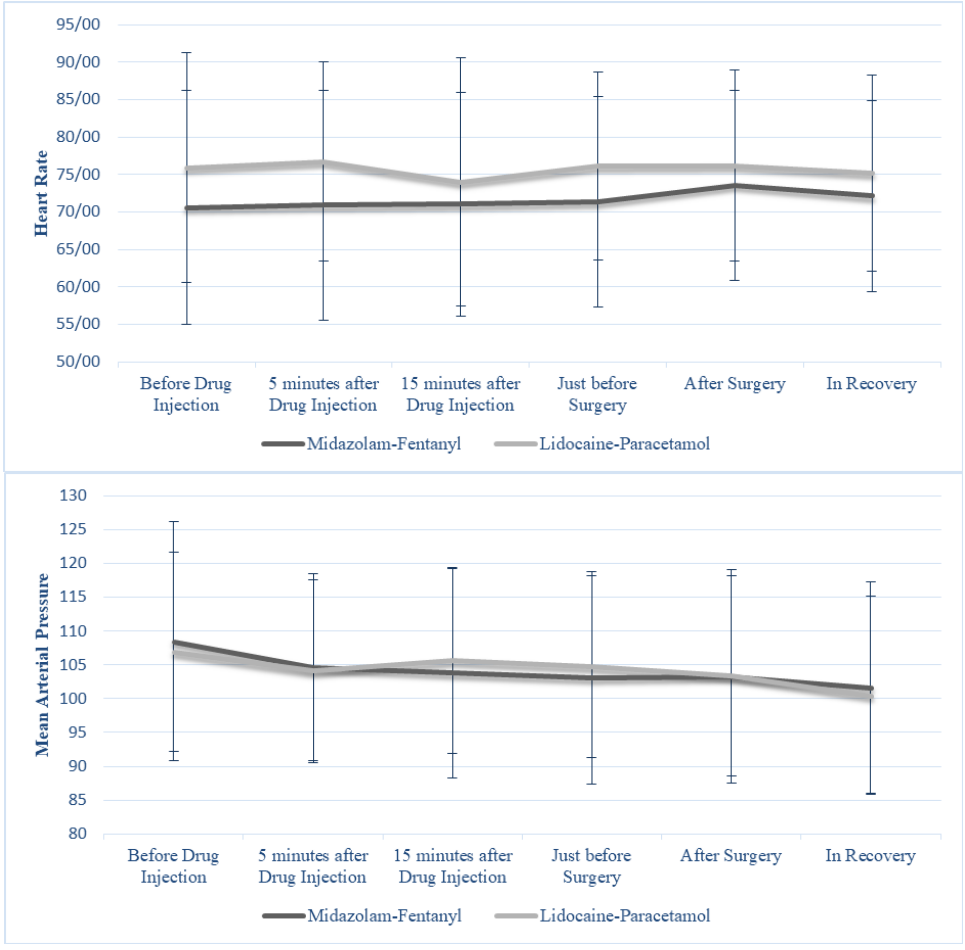

Figure 2. Comparing the hemodynamic variables

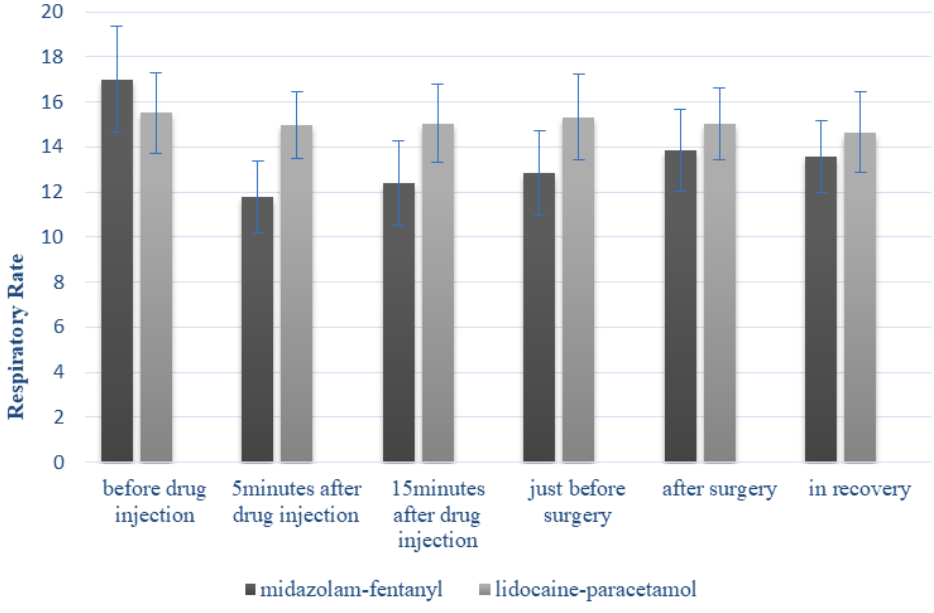

Figure 3. Comparing the mean respiratory rate of patients in time intervals in Lidocaine/Paracetamol (LP) and Midazolam/Fentanyl (MF) groups

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The results of this study revealed that using lidocaine-paracetamol as a supplemental approach for patients undergoing cataract surgery under topical anesthesia has better sedation scores compared to using midazolam-fentanyl, although both of them (lidocaine-paracetamol and midazolam-fentanyl) decreased the pain scores in the same manner. Furthermore, in the MF group, respiratory depression was significantly higher than in the LP group.

According to the review of the related literature and according to the author's knowledge, no study had been conducted in the form of a double-blinded clinical trial comparing the effects of LP and MF; however, some studies were conducted to examine paradoxical conclusions on the effects of paracetamol in cataract surgery.

In this regard, partially by the results, Alipour et al showed that no significant difference was observed between the paracetamol and fentanyl groups in the mean score of long-term and postoperative pain and anxiety scores [4]. They suggested that paracetamol can be used as an effective analgesic agent for postoperative pain in patients undergoing cataract surgery without any side effects [4]. In addition, Connolly KP et al declared that the inclusion of intravenous acetaminophen as part of a multimodal pain regimen led to fewer episodes of delirium in geriatric patients [6]. Reduced opioid use immediately after surgery may play a major role in this outcome. Lower delirium rates may reduce the utilization of inpatient resources and the duration of hospital stays [6]. On the other hand, it is suggested that intravenous lidocaine produces analgesia via direct or indirect interaction with Na^+ channels, different receptors, and nociceptive transmission pathways [10]. Koppert et al declared that lidocaine provides analgesia during surgery and decreases central hyperalgesia by its effect on mechano-sensitive receptors [11].

Besides the nervous system, local anesthetics have a positive influence on the inflammatory response and the hemostatic system [12].

Therefore, we assume that the combination of lidocaine and paracetamol is a justified choice as a supplementary approach for patients undergoing cataract surgery under topical anesthesia.

In the present study, we selected a dose of lidocaine and paracetamol within the common dose range used by other studies for postoperative pain relief [10, 13]. This dosage of lidocaine is a reasonable dose between efficacy and toxicity in previous studies [14, 15].

Another crucial finding of the present study that should be emphasized is that the rate of respiratory depression in the LP group was lower than in the MF group, in which is consistent with the previous studies [4, 6]. However, the combined use of benzodiazepines and narcotics increases the risk for potentially troublesome respiratory depression [3].

Considering the stability of patients during recovery, the subjects in the LP group did not experience any restlessness.

The other finding which should be considered is that surgeon and patient satisfaction was reported at the same level in both groups. Moreover; in a meta-analysis conducted by Vigneault et al., the effect of intravenous lidocaine on postoperative pain was investigated, and the results showed that, in addition to reducing postoperative pain, nausea and vomiting, length of hospitalization, as well as cardiac and neurologic complications were decreased [16]. Although all trials included in this meta-analysis involved patients undergoing general anesthesia, the results were partially consistent with the findings of the present study, in which postoperative pain was reported as similar in both the LP and MF groups.

The last observation that should be noted is that the hemodynamic variations were the same in both groups. The possible explanation for these results may be the good management of patients' sedation scores with the administration of additional propofol, although the amount of additional propofol administration was insignificant in both groups. The weakness of this study was the small sample size. The strength of this study includes the validity of the randomized controlled trial methodology, the integrity of data collection, and close monitoring of patients for adverse events.

Further studies are necessary to determine the most effective approach to manage patients undergoing cataract surgery under topical anesthesia.

5. Conclusion

The use of lidocain-pracetamol as a supplementary approach for patients undergoing cataract surgery under topical anesthesia could cause better sedation scores compared to the use of midazolam-fentanyl. And it is a safe, cheap multimodal approach for the management of patients during cataract surgery using topical anesthesia with lower respiratory depression.

Ethical Considerations

Compliance with ethical guidelines

This study was registered at Iranian clinical trial registering :IRCT registration number: IRCT20181027041480N1.

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The paper was extracted from the residency thesis of the third author.

Authors' contributions

Conceptualization: Marzieh Beigom Khezri and Mohammad Reza Oladi: Study design: Nasim Zarrin, Marzieh Beigom Khezri and Mohammad Reza Oladi; Data acquisition and drafting the manuscript: Raheleh Safaei; Revising the manuscript critically for important intellectual content: Marzieh Beigom Khezri

Conflict of interest

The authors declare no conflict of interest.

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