Int J Physiol Pathophysiol Pharmacol 2022;14(6):316-323
www.ijppp.org /ISSN:1944-8171/IJPPP0145051

Original Article

Evaluating the preventive effect of metoclopramide and aminophylline on pain after deep vitrectomy

Darioush Moradi Farsani[1], Aryan Rafieezadeh[2], Niloofaralsadat Nourian[3], Hossein Mohammadi[2], Khosro Naghibi[1], Kamal Saghir[2]

[1]Department of Anesthesiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [2]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; [3]School of Medicine, Islamic Azad University of Najaf Abad Branch, Isfahan, Iran

Received June 30, 2022; Accepted November 14, 2022; Epub December 15, 2022; Published December 30, 2022

Abstract: Background: Deep vitrectomy is one of the most frequently performed ophthalmic procedures. Postoperative pain is a common complaint among patients. Consequently, we investigated whether metoclopramide and aminophylline could decrease pain intensity following deep vitrectomy. Methods: This double-blinded clinical trial study that was approved by the Ethical Committee of Isfahan University of Medical Sciences (IR.MUI.REC.1396.3.217) (Thesis Reg. number: 396217) and registered at the Iranian Registry of Clinical Trials (IRCT) (Reg. number: IRCT20170716035104N5, available at https://www.irct.ir/trial/59146) aimed to evaluate 105 patients who were candidates for deep vitrectomy. They were randomly assigned into three groups: metoclopramide (received 0.1 mg/kg diluted in 10 ml of normal saline), aminophylline (received 4 mg/kg diluted in 10 ml of normal saline), and placebo (received 10 ml of normal saline). Postoperative pain was evaluated in all groups. Results: The postoperative pain levels of the three groups differed significantly from the start of the recovery to 30 minutes, 60 minutes, 2 hours, and 4 hours postoperatively, with metoclopramide and aminophylline groups experiencing less postoperative pain than the placebo group. Moreover, there was a significant difference between the groups regarding patient satisfaction ($P<0.05$). Conclusion: Both metoclopramide and aminophylline significantly reduce postoperative pain after deep vitrectomy, although metoclopramide has a greater effect.

Keywords: Postoperative pain, vitrectomy, metoclopramide, aminophylline

Introduction

Vitrectomy is one of the most common ophthalmic surgeries performed to enhance vitreous transparency, and its major indications are rhegmatogenous retinal detachment, trauma, diabetic retinopathy, and proliferative sickle cell retinopathy [1]. Although no studies have stated any absolute contraindications for vitrectomy, it seems that the presence of intraocular adhesive tumors such as retinoblastoma is proposed as a relative contraindication (considering the possibility of inducing the seeding process). However, a multidisciplinary approach is usually based on individual characteristics [2, 3].

There are currently two types of surgery: anterior and deep vitrectomy [4, 5]. Deep vitrectomy might be associated with intra- and postoperative complications [6, 7]. Postoperative pain is a considerable complication in ophthalmic surgery patients, especially vitrectomy [8, 9]. Some studies suggest that 75% of patients experience pain after vitrectomy, and 30% complain about moderate or severe postoperative pain [10-12]. Postoperative pain could be associated with several problems, including respiratory complications, increased metabolism level, development of salt and water retention, high blood pressure, tachycardia, dysrhythmia, ischemia or myocardial infarction, gastrointestinal disorders, thromboembolic events, anxiety and sleep disorders, which in turn can increase the overall cost of hospitalization, so appropriate analgesics can help control such complications and thus improve the quality of care and patient satisfaction [13-15]. Preventive analgesia is one of the well-known strategies that can effectively reduce pain and alter the central and peripheral sensitization before surgical tis-

sue damage, thus achieving a better result [16]. However, these methods might demonstrate their side effects, including hemodynamic changes; therefore, the analgesic agent should develop effective anesthetic outcomes, sustain hemodynamic stability, and prevent postoperative pain [17-20]. While opioids are among the most frequently prescribed analgesics, concerns about their side effects make their usage controversial [21]. Metoclopramide has been widely used as an anti-emetic agent in nausea and emetic disorders associated with the gastrointestinal system [22]. Moreover, metoclopramide also affects postoperative analgesia and the need for analgesic agents [22]. Some recent investigations have demonstrated the analgesic effects of metoclopramide and its decreasing impact on the need for postoperative analgesia [22]. It has been noted that metoclopramide increases other analgesic absorption by facilitating gastric emptying, which suggests that it could be used as a pain reliever [23]. However, the mechanisms of such effects remain unclear [24]. Aminophylline is a derivate of xanthine, which causes dilation in the smooth muscles of the bronchi and bronchodilation by inhibiting the xanthine oxidase enzyme [25]. It has been reported that aminophylline has analgesic properties. For example, a recent report indicated that aminophylline could reduce headaches after dural punctures [25]. In another study, aminophylline reduced ischemic heart pain by antagonizing adenosine receptors during transluminal coronary angioplasty [26].

As of yet, there has been no research comparing aminophylline and metoclopramide in reducing pain intensity after deep vitrectomy surgery. To fill such a void, the purpose of the study was to compare the effectiveness of these two agents at reducing pain after an invasive vitrectomy.

Materials and methods

According to the study criteria, in this randomized, double-blind, controlled clinical trial, we selected 105 candidates for deep vitrectomy surgery and were referred to Feiz Hospital in Isfahan from 2016 to 2017. Inclusion criteria were patients undergoing pars plana deep vitrectomy (20G) surgery, age between 18 and 75 years, status classification I or II according to the American Society of Anesthesiologists (ASA) Status Classification System, body mass index (BMI) less than 35, ability to speak, and written informed consent to participate. Exclusion criteria were patients with a history of consumption of corticosteroids and immunosuppressants since one month before surgery, a previous history of allergies to metoclopramide or aminophylline, consumption of metoclopramide, aminophylline or any analgesics 24 or less than 24 hours before surgery, history of malignancy, uncontrolled diabetes, smoking cigarettes, addictive drugs, and alcohol abuse, chronic pain for more than six months, mental illness, evident preoperative anxiety, or tachycardia, history of consumption of anti-anxiety or anti-arrhythmic medications, and a history of general anesthesia, by using volatile anesthetics, in the last six months. Moreover, in case of undesired complications during the surgical procedure, such as hemodynamic disorders, cardiac arrest, etc., and if a change in anesthesia or surgery technique was required during the surgical operation, or if the surgery lasted more than 150 minutes or less than 60 minutes, the patient was excluded from the study. The patient demographics (including age, gender, and BMI) were collected initially by reviewing their medical records.

The administration of the study drugs

Patients in the first group received metoclopramide, those in the second group received aminophylline, and those in the third group received a placebo. A ten-minute intravenous infusion of 0.1 mg/kg metoclopramide diluted in 10 ml of sterile normal saline was administered to patients in the first group fifteen minutes before the end of the operation. For patients in the second group, 4 mg/kg aminophylline diluted in 10 ml of normal saline solution was infused intravenously over 10 minutes. The placebo group received 10 ml of sterile normal saline, similar to the previous groups. Each group was subjected to the same method of induction of anesthesia. Patients were anesthetized with sodium thiopental 5 mg/kg, fentanyl 2 mcg/kg, and atracurium 0.5 mg/kg (Rescue analgesia was administered at a quarter of the dose if required). Anesthesia was maintained in all groups using 1.2% isoflurane and a mixture of oxygen and nitrous oxide (1:1 ratio). The intravenous infusion of ringer

lactate solution was given to all patients before anesthesia was induced to prevent hypotension. Approximately 15 minutes before the end of the surgery, the metoclopramide group received a slow infusion of 0.1 mg/kg metoclopramide under the surgeon's coordination. In the aminophylline group, patients received 4 mg/kg of aminophylline intravenously within 10 minutes. Before injection, metoclopramide and aminophylline were diluted in 10 ml of normal saline solution. Lastly, patients in the placebo group received 10 ml of normal saline intravenously. Intravenous fluids were administered first if the systolic blood pressure decreased by more than 20% of the baseline values before anesthesia induction or the heart rate fell below 40 beats per minute. As a last resort, ephedrine or atropine was administered if there was no response. We considered lowering the doses of anesthesia drugs in cases of hypotension that did not respond well to the fluid replacement or bradycardia treatment.

Pre and intraoperative assessment

In each group, the isoflurane was discontinued after surgery, and the N_2O usage ended after the eye dressing. During this time, 100% oxygen was supplied to the lungs at a flow rate of 4 liters per minute until spontaneous ventilation started. The neuromuscular block was reversed by administering 0.04 mg/kg neostigmine and 0.02 mg/kg atropine, and the patient was eventually extubated and awoke.

The patients were admitted to the Postanesthesia Care Unit (PACU) after surgery and then to the ophthalmology department upon recovery (according to The Modified Aldrete Score). The Modified Aldrete Score is a valuable tool that measures the suitability for discharge from PACU by assessing the patient's motor activity, breathing status, circulation, consciousness, and peripheral O_2 saturation (scores are between 0 and 12). A score of at least nine was required for discharge from the PACU.

Postoperative assessment

In the PACU, the pain intensity score was evaluated and recorded according to the Visual Analogue Scale (VAS). An assessment of pain intensity is measured by a 10 cm line within two endpoints, which are 0 (no pain) and 10 (pain as bad as it can be). Patients can indicate their pain level by placing a mark on a specific line. A VAS was measured upon admission to the PACU, then 30, 60, two, four, eight, 16, and 24 hours later. We also measured hemodynamic variables, such as mean arterial blood pressure, heart rate, and respiratory rate, before induction, during surgery (once), and in the PACU (after surgery). When patients' VAS pain intensity scores exceeded three, 0.5 mg/kg of intravenous pethidine was injected. Twenty-four hours following the PACU admission, patients were assessed for the total number of rescue analgesics used, recovery time, and satisfaction. We used a one-item questionnaire based on a four-point Likert scale (as completely satisfied, relatively satisfied, relatively dissatisfied, and ultimately dissatisfied) to assess patient satisfaction.

Ethical considerations

The conductor thoroughly explained the study's purpose and provided all the necessary information before all patients signed an informed consent form. The study was double-blinded, which meant that an anesthesiologist who was unaware of the study method prepared similar syringes and labeled them with numbers provided by the study conductor. Additionally, patients were unaware of the type of medication they were receiving.

Statistical analysis

For this study, the sample size was determined using the estimating sample size method for the comparison of two means, considering the 95% confidence level, 80% power [(z1-a/2 = 1/196), (z1-b = 0.84)], the standard deviation of postoperative pain intensity (which was equal to 1.17) and the minimum significant difference between the groups (estimated to be 0.8); each group consisted of 34 patients. For more assurance, we included 35 patients in each group, (a total of 105 participants). Using Random Allocation Software, patients were randomly allocated to three study groups, based on study criteria. We used IBM SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) for the final analysis. The qualitative data was displayed as frequency and percentage, while the quantitative data were expressed as mean and standard deviation. In order to compare and analyze the data in study groups,

Table 1. Demographic information of patients in the three study groups

Variable		Metoclopramide group	Aminophylline group	Placebo group	*P*-value
Number		35	35	35	-
Gender	Male	16 (47.5%)	19 (54.3%)	23 (65.7%)	0.24*
	Female	19 (54.3%)	16 (45.7%)	12 (34.3%)	
Age (Years)		60.34±13.39	62.45±12.03	59.80±12.45	0.65**
BMI (kg/m^2)		25.28±3.82	26.30±3.76	24.30±3.64	0.08**

*Using chi-square test, **Using One-way ANOVA.

Table 2. Postoperative pain at different time intervals in three study groups

VAS	Metoclopramide group	Aminophylline group	Placebo group	*P*-value*
Upon the PACU admission	4.91±0.71	5.48±0.95	6.57±1.11	<0.001
30 minutes later	5.50±0.74	6.17±0.95	7.20±1.20	<0.001
60 minutes later	6.17±1.05	6.88±1.25	7.87±1.29	<0.001
2 hours later	6.02±0.86	6.17±1.33	7.61±1.39	<0.001
4 hours later	4.67±1.24	5.08±1.54	6.02±1.26	<0.001
8 hours later	3.05±0.98	3.32±1.12	3.55±0.92	0.13
16 hours later	1.23±1.10	1.55±1.25	1.52±1.21	0.46
24 hours later	0.79±0.94	0.97±1.19	0.94±1.12	0.77

*Using One-way ANOVA.

Chi-Square tests and One-way ANOVA tests were used. Additionally, quantitative data changes at different points in time were compared using the Repeated Measure ANOVA test. In this study, a *p*-value less than 0.05 indicated a statistically significant difference.

Results

Study population

Three groups of 35 patients were included in this study: metoclopramide (16 males and 19 females), aminophylline (19 males and 16 females), and placebo (23 males and 12 females). No significant differences were found between the groups regarding gender, age, or BMI (P>0.05) (**Table 1**).

Pain and hemodynamic data

Each patient's mean arterial blood pressure, heart rate, and respiratory rate were recorded. Before induction of anesthesia, before surgery, in the PACU, and eight hours postoperatively, there was no statistically significant difference between the groups regarding mean arterial blood pressure, heart rate, and respiratory rate (P>0.05). Statistically significant differences were found between groups based on postoperative pain at the beginning of recovery, 30 and 60 minutes later, and 2 and 4 hours later. These findings indicate that postoperative pain was lower for the metoclopramide and aminophylline groups than for the placebo group. However, there was no significant difference between groups based on pain at eight, 16, and 24 hours after surgery (P>0.05) (**Table 2**). Variations in VAS at different time intervals were significantly different between the study groups according to the repeated measures ANOVA (**Table 2**).

Further assessments

The need for a rescue analgesic (pethidine) and recovery time did not differ significantly between the groups (P>0.05). Nonetheless, there was a significant difference between the groups regarding patient satisfaction, as metoclopramide and aminophylline were associated with significantly higher levels of patient satisfaction than placebo (P = 0.04) (**Table 3**).

Discussion

Our findings demonstrated that metoclopramide and aminophylline remarkably reduced postoperative pain among patients undergoing deep vitrectomy surgery. Metoclopramide, how-

Table 3. Need for pethidine, patient satisfaction, and recovery time in the three study groups

Variable		Metoclopramide group	Aminophylline group	Placebo group	*P*-value
Need for rescue analgesic (pethidine)		8 (22.9%)	11 (31.4%)	14 (40%)	0.30*
Patient satisfaction	Completely satisfied	15 (42.9%)	14 (41.2%)	9 (25.7%)	0.04*
	Relatively satisfied	14 (40%)	16 (47.1%)	10 (28.6%)	
	Relatively dissatisfied	5 (14.3%)	3 (8.8%)	12 (34.3%)	
	Completely dissatisfied	1 (2.9%)	1 (2.9%)	4 (11.4%)	
Recovery time		35.50±5.73	34.63±7.66	37.11±6.41	0.30**

*Using chi-square test, **Using One-way ANOVA.

ever, reduced postoperative pain more effectively than aminophylline. Even though both drugs effectively reduced the need for rescue analgesia, this difference was insignificant, indicating that patients were relatively satisfied after receiving aminophylline and metoclopramide. Neither of these drugs significantly altered hemodynamics in patients, and neither showed side effects in patients who received them. One study investigated the effect of metoclopramide as a pain reliever after eye surgery on migraine headaches in two patients. Both patients in this study suffered from migraines and pain following ocular procedures, and both improved after receiving intravenous metoclopramide within two minutes. It was suggested by the authors that metoclopramide could be advantageous in reducing postoperative pain [27]. In our study, both drugs effectively reduced postoperative pain, but metoclopramide was more effective to a lesser extent.

Heidari and colleagues studied patients undergoing septorhinoplasty. The researchers administered one group of patients 10 mg of metoclopramide and 0.3 mg/kg of ketamine, and the other group received only 0.3 mg/kg of ketamine (intravenously, 5 minutes before surgery). They found that postoperative pain and the need for rescue analgesia were significantly lower in the metoclopramide group than in the control group. Our results confirm previous findings. There were also fewer cases of nausea and vomiting in their metoclopramide group compared to the control group. As a result, they concluded that metoclopramide and ketamine could be combined to reduce postoperative pain in the absence of contraindications [28]. Likewise, another study found that adding 10 mg/kg of metoclopramide to 5 ml of 2% lidocaine was more effective in reducing post-episiotomy pain than using lidocaine alone. Based on the results, combination therapy improved pain reduction after episiotomy more than lidocaine alone [29]. In line with these findings, we found similar results in our study.

Interestingly, two other studies have evaluated metoclopramide's analgesic effects in postoperative pain compared to tramadol, demonstrating its value as a potential analgesic [30, 31]. A study comparing the effects of metoclopramide and ketamine on reducing postoperative pain in 86 patients undergoing abdominal surgery under general anesthesia suggested that intravenous metoclopramide was more effective at reducing postoperative pain than ketamine before induction of anesthesia [32]. Compared with metoclopramide, little research has been conducted on the effect of aminophylline on postoperative pain. One study prolonged propofol's postoperative sedative effects were prolonged by aminophylline [33]. In another study, oral aminophylline was found to improve exercise-induced pain thresholds in patients with X syndrome and was also found to improve clinical symptoms and ST-segment changes in electrocardiograms [26]. Regardless, to date, no similar research has been found to evaluate the effects of aminophylline on postoperative pain at the time of preparing this manuscript.

According to our results, aminophylline and metoclopramide are useful drugs that effectively reduce postoperative pain and the need for analgesics in patients undergoing deep vitrectomy and are without remarkable side effects. This is the first study to compare metoclopramide and aminophylline on post-vitrectomy pain. We believe the present study is unique in that it evaluates the prevention effects of metoclopramide and aminophylline on pain

after deep vitrectomy, which can help guide future interventional studies and assist in selecting appropriate tools for assessing pain after deep vitrectomy. Despite large amounts of research identifying factors and techniques that affect hemodynamics and pain control during and after deep vitrectomy surgery [34-37], many physiological and pathophysiological pathways underlying pain-related mechanisms remain vague, provoking controversy among researchers. According to our biased experience, considering the high rates of narcotic analgesic use, their numerous side effects, the availability of non-narcotic analgesics (especially in Iran's medical centers), and the fewer side effects of aminophylline and metoclopramide, we believe the non-narcotic analgesics mentioned above could be used more often. It is also recommended that narcotics be spared from use in cases where these two drugs are contraindicated or if they do not seem to be effective.

It is noteworthy that the present study has several limitations, including:

- A relatively small sample size.
- A short follow-up period.
- The relatively wide range of participants (ages 18 to 75).
- The single-center setting in which this study was conducted.

The above results should be interpreted cautiously, as it would be prudent to do so since similar studies have not been conducted previously, and many remarkable factors have limited our findings. Further extensive studies with a greater sample size are recommended to clarify the current gaps in this field.

Conclusion

Both metoclopramide and aminophylline significantly reduce postoperative pain after deep vitrectomy, although metoclopramide has a greater effect. These data could have high clinical importance.

Acknowledgements

The authors would like to express their warmest gratitude towards the efforts of Dr. Roham Nik Khah and Dr. Nasrin Sanjari who provided valuable technical and scientific information. We also thank all of the hardworking personnel of Feiz hospital in Isfahan city for their efforts regarding the conduction of this research.

Disclosure of conflict of interest

None.

Address correspondence to: Khosro Naghibi, School of Medicine, Isfahan University of Medical Science, Hezar Jarib Street, Isfahan 8174673461, Isfahan, Iran. Tel: +989130609558; Fax: +9836684510; E-mail: naghibi@med.mui.ac.ir

References

[1] Okonkwo ON, Lewis K, Hassan AO, Gyasi ME, Oluyadi B, Ogunro A, Oderinlo O and Ulaikere M. Indications and outcomes of vitrectomy surgery in a series of 1000 black African eyes. BMJ Open Ophthalmol 2019; 4: e000083.

[2] Ancona-Lezama D, Dalvin LA and Shields CL. Modern treatment of retinoblastoma: a 2020 review. Indian J Ophthalmol 2020; 68: 2356-2365.

[3] Keyal K, Liao X, Liu G, Yang S and Wang F. Post-vitrectomy cataract acceleration in phakic eyes: a review. Discov Med 2017; 24: 305-311.

[4] Diabetic Retinopathy Clinical Research Network Writing Committee, Haller JA, Qin H, Apte RS, Beck RR, Bressler NM, Browning DJ, Danis RP, Glassman AR, Googe JM, Kollman C, Lauer AK, Peters MA and Stockman ME. Vitrectomy outcomes in eyes with diabetic macular edema and vitreomacular traction. Ophthalmology 2010; 117: 1087-1093, e3.

[5] Gao X, Ikuno Y, Fujimoto S and Nishida K. Risk factors for development of full-thickness macular holes after pars plana vitrectomy for myopic foveoschisis. Am J Ophthalmol 2013; 155: 1021-1027, e1.

[6] Brown EN, Purdon PL and Van Dort CJ. General anesthesia and altered states of arousal: a systems neuroscience analysis. Annu Rev Neurosci 2011; 34: 601-628.

[7] Rahimi Varposhti M, Moradi Farsani D, Ghadimi K and Asadi M. Reduction of oculocardiac reflex with tetracaine eye drop in strabismus surgery. Strabismus 2019; 27: 1-5.

[8] Fekrat S, Elsing SH, Raja SC, Campochiaro PA, de Juan E Jr and Haller JA. Eye pain after vitreoretinal surgery: a prospective study of 185 patients. Retina 2001; 21: 627-632.

[9] Moradi Farsani D, Ghadimi K, Abrishamkar R, Montazeri K and Peyman A. Evaluating sedative effects of dexmedetomidine and morphine

in the patients with opioid use disorder undergoing cataract surgery. Am J Clin Exp Immunol 2021; 10: 30-36.
[10] Fletcher D, Fermanian C, Mardaye A and Aegerter P; Pain and regional anesthesia committee of the French Anesthesia and Intensive Care Society (SFAR). A patient-based national survey on postoperative pain management in France reveals significant achievements and persistent challenges. Pain 2008; 137: 441-451.
[11] Benhamou D, Berti M, Brodner G, De Andres J, Draisci G, Moreno-Azcoita M, Neugebauer EA, Schwenk W, Torres LM and Viel E. Postoperative analgesic therapy observational survey (PATHOS): a practice pattern study in 7 central/southern European countries. Pain 2008; 136: 134-141.
[12] Awan H and Durrani Z. Postoperative pain management in the surgical wards of a tertiary care hospital in Peshawar. J Pak Med Assoc 2015; 65: 358-361.
[13] Morgan B and Stanik-Hutt J. Utilization of a preemptive, multimodal analgesic regimen in adult ambulatory septoplasty patients: a quality improvement project. ORL Head Neck Nurs 2015; 33: 6-13.
[14] Sadrolsadat SH, Yousefshahi F, Ostadalipour A, Mohammadi FZ and Makarem J. Effect of intravenous acetaminophen on postoperative pain in vitrectomy: a randomized, double-blind, clinical trial. Anesth Pain Med 2017; 7: e13639.
[15] Vasilopoulos T, Wardhan R, Rashidi P, Fillingim RB, Wallace MR, Crispen PL, Parvataneni HK, Prieto HA, Machuca TN, Hughes SJ, Murad GJA and Tighe PJ; Temporal Postoperative Pain Signatures (TEMPOS) Group. Patient and procedural determinants of postoperative pain trajectories. Anesthesiology 2021; 134: 421-34.
[16] Doleman B, Read D, Lund JN and Williams JP. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analysis. Reg Anesth Pain Med 2015; 40: 706-12.
[17] Kampe S, Geismann B, Weinreich G, Stamatis G, Ebmeyer U and Gerbershagen HJ. The influence of type of anesthesia, perioperative pain, and preoperative health status on chronic pain six months after thoracotomy-a prospective cohort study. Pain Med 2017; 18: 2208-2213.
[18] Angst MS. Intraoperative use of remifentanil for TIVA: postoperative pain, acute tolerance, and opioid-induced hyperalgesia. J Cardiothorac Vasc Anesth 2015; 29 Suppl 1: S16-S22.
[19] de Hoogd S, Ahlers SJGM, van Dongen EPA, van de Garde EMW, Daeter EJ, Dahan A, Tibboel D and Knibbe CAJ. Randomized controlled trial on the influence of intraoperative remifentanil versus fentanyl on acute and chronic pain after cardiac surgery. Pain Pract 2018; 18: 443-451.
[20] Haddad S, Ghadimi K, Abrishamkar R and Asl NSM. Comparing laparoscopy and laparotomy procedures in the radical hysterectomy surgery for endometrial cancer: a basic review. Am J Transl Res 2021; 13: 2456-2461.
[21] De Oliveira GS Jr, Castro-Alves LJ and McCarthy RJ. Single-dose systemic acetaminophen to prevent postoperative pain: a meta-analysis of randomized controlled trials. Clin J Pain 2015; 31: 86-93.
[22] Pang W, Liu YC, Maboudou E, Chen TX, Chois JM, Liao CC and Wu RS. Metoclopramide improves the quality of tramadol PCA indistinguishable to morphine PCA: a prospective, randomized, double blind clinical comparison. Pain Med 2013; 14: 1426-1434.
[23] Shakhatreh M, Jehangir A, Malik Z and Parkman HP. Metoclopramide for the treatment of diabetic gastroparesis. Expert Rev Gastroenterol Hepatol 2019; 13: 711-721.
[24] Pang W, Liu YC, Maboudou E, Chen TX, Chois JM, Liao CC and Wu RS. Metoclopramide improves the quality of tramadol PCA indistinguishable to morphine PCA: a prospective, randomized, double blind clinical comparison. Pain Med 2013; 14: 1426-1434.
[25] Pokorna A, Bobal P, Oravec M, Rarova L, Bobalova J and Jampilek J. Investigation of permeation of theophylline through skin using selected piperazine-2,5-diones. Molecules 2019; 24: 566.
[26] Cooney L, Sinha I and Hawcutt D. Aminophylline dosage in asthma exacerbations in children: a systematic review. PLoS One 2016; 11: e0159965.
[27] Ha H and Gonzalez A. Migraine headache prophylaxis. Am Fam Physician 2019; 99: 17-24.
[28] Heidari SM, Khalili G, Roohani S and Mehrabi Koushki A. Comparing the effects of ketamine alone and in combination with metoclopramide on postoperative pain. J Isfahan Med Sch 2013; 30: 2441-2449.
[29] Shabanian S, Kalbasi S, Shabanian G, Khoram B and Ganji F. The effect of metoclopramide addition to lidocaine on pain of patients with grades II and III post-episiotomy repair. J Clin Diagn Res 2017; 11: QC11-QC14.
[30] Beakley BD, Kaye AM and Kaye AD. Tramadol, pharmacology, side effects, and serotonin syndrome: a review. Pain Physician 2015; 18: 395-400.
[31] Ceyhan A, Ustun H, Altunatmaz K, Ide T and Unal N. Is metoclopramide an alternative to tramadol in management of post-operative pain? An experimental study. J Vet Med A Physiol Pathol Clin Med 2005; 52: 249-253.

[32] Heydari SM, Hashemi SJ and Pourali S. The comparison of preventive analgesic effects of ketamine, paracetamol and magnesium sulfate on postoperative pain control in patients undergoing lower limb surgery: a randomized clinical trial. Adv Biomed Res 2017; 6: 134.
[33] Sakurai S, Fukunaga A, Fukuda K, Kasahara M, Ichinohe T and Kaneko Y. Aminophylline reversal of prolonged postoperative sedation induced by propofol. J Anesth 2008; 22: 86-88.
[34] Adinehmehr L, Shetabi H, Moradi Farsani D, Salehi A and Noorbakhsh M. Comparison of the sedation quality of etomidate, propofol, and midazolam in combination with fentanyl during phacoemulsification cataract surgery: a double-blind, randomized, controlled, clinical trial. Anesth Pain Med 2019; 9: e87415.
[35] Moradi D, Naghibi K, Alikiaii B and Mashayekhi Z. Comparison of the effects of intravenous phenylephrine and ephedrine in treatment of hypotension after spinal anesthesia in orthopedic surgery. J Babol Univ Medical Sci 2016; 18: 21-27.
[36] Moradi-Farsani D, Heydari SM and Nazemroaya B. The effect of subcutaneous injection of metoclopramide, pethidine, and ketamine on postoperative pain after inguinal hernia repair under general anesthesia. J Isfahan Med Sch 2020; 38: 252-9.
[37] Nazemroaya B, Ghosouri A, Honarmand A and Hashemi ST. Comparison of hemodynamic changes and serum potassium levels in the use of succinylcholine and cisatracurium in electroconvulsive therapy. J Res Med Sci 2021; 26: 106.