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Research Article

Effect of Alfentanil on postoperative shivering after Cataract surgeries: a randomised, double-blind clinical trial.

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ABSTRACT

BACKGROUND: Postoperative shivering is one of the most common complications in patients recovering from general anaesthesia. Although a variety of pharmacological therapies have been used to control postoperative shivering, no ideal drug has been found to date.

OBJECTIVES: The aim of this study was to compare the efficacy and accompanying side-effects of Alfentanil and comparing that with the conventional ant shivering drug: pethidine for the prevention of postoperative shivering.

DESIGN: A randomised, double-blind clinical study.

Material and Methods: One hundred and thirty five adult patients, ASA 2 or 3, aged 65 years or older are scheduled for elective Cataract surgery under general anaesthesia.

The patients were allocated randomly to receive Alfentanil 500 micrograms (Group A, n=45), Pethidine 25mg (Group P, n=45) or Normal Saline (Group S, n=45) 20min before the end of surgery. The primary outcome was measured with the incidence and severity of postoperative shivering.

Results: The groups differ significantly regarding occurrence and severity of shivering. Both opioids were effective in prevention of postoperative shivering but not in a similar extent.

Conclusion: We conclude that Alfentanil 500 micrograms was effective in the prevention of post-anaesthetic shivering after general anaesthesia without significant side effects but it is not as effective as Pethidine.

Keywords: postoperative shivering, Alfentanil, Pethidine, randomized clinical trial

INTRODUCTION:

Post anesthetic shivering is an accompanying part of general anesthesia, with an estimated rate up to 60% and has different unpleasant and stressful consequences for patients undergoing surgery due to some physiological changes including increasing oxygen consumption, hypoxemia, lactic acidosis, and hypercarbia (1 , 2). These changes, in addition to increasing intraocular and

intracranial pressure, may complicate the recovery process during anesthesia and increase the wound pain (3). The major cause of postoperative shivering is core hypothermia due to anesthesia-induced heat distribution, evaporation, and radiation during surgery; however, even if the patient's core temperature is carefully maintained, anaesthetics-induced shivering still develops (4).

Therefore, prevention of shivering is important, especially in elderly and ischemic heart disease patients (5). The goal of this study was to compare the effect of Alfentanil, or Pethidine (meperidine), on prevention of shivering in patients undergoing Cataract surgeries under general anesthesia.

Pethidine (meperidine) is a well-known effective drug for prevention and treatment of shivering (6). Chiang MH et al demonstrated that the minimum effective dose of Meperidine for post anesthesia shivering prevention was 0.35 mg/kg with 75% sensitivity and 60% specificity (7).

Pethidine is an opioid that gains its popularity for the effective pain control through acting on the opioid-receptors (8). However, Pethidine sometimes brings about unfavourable side effects that largely limit its clinical utility such as nausea, vomiting and hypotension (8,9 and 10). In patients with impaired renal and liver function, Pethidine may cause excitatory central nervous system (CNS) effects through its neurotoxic metabolite, norpethidine, resulting in irritability and seizure attack (11). On the contrary, though not clinically apparent, Pethidine potentially causes inhibitory impacts on the CNS and impairs normal cerebellar and oculomotor function in the short term (12).

Therefore, it seems that proper alternatives should be determined for cases with contraindications for Pethidine administration.

Alfentanil is an opiate analgesic and few studies have been conducted on reducing shivering after anesthesia but on the other hand these studies have reported confusing and controversial results, in some studies Alfentanil have been recognized as a superior drug ,while Pethidine is reported to be superior in some other (13-15). We compared Alfentanil with Meperidine for efficacy in the prevention of shivering during Isoflurane anesthesia.

The purpose of this study was to determine whether very low-dose of Alfentanil could prevent the development of Isoflurane-induced shivering.

MATERIALS AND METHODS

One hundred and thirty five ASA II and III adult patients either sex, aged 65 years or older receiving general anesthesia scheduled to undergo Cataract surgeries were recruited for this randomized, double-blind, clinical trial study. Approval by the institutional review board and written informed consent from each patient were obtained. The number of patients required in each group was determined using power analysis based on previous study. Incidence of post aesthetic shivering was estimated to be around 60%. The sample size required detecting 40% reduction at 5% level of significance and 80% power was 42 patients in each group but we recruited 45 patients per group to compensate for any exclusion.

Patients with obesity (body mass index (BMI) >35), history of convulsions, neuromuscular disease, allergies, were not included for the study. Patients whose first temperature reading on placing temperature probe intraoperatively, was found to be less than 36°C or greater than 38°C and those requiring large volume of crystalloid fluids (>2 L) to maintain blood pressure were excluded. Before induction of anaesthesia, the patients were given 10 ml/kg of a Ringer lactate serum. To maintain the integrity of results, none of the patients received pre anesthetic medication.

Patients were randomly assigned to one of three groups using a computer-generated randomization schedule to receive intravenous (IV) Alfentanil 500 µg (Group A), or Pethidine 25 mg (Group P), or the same volume of Normal Saline (Group S) 5 minutes before the anticipated completion of surgery. All three drugs were prepared in the same 5 cc syringes and the anesthesiologist responsible for the control and registration of the clinical symptoms was blinded to the study drugs.

Induction of anesthesia started with the same way in three groups by injecting fentanyl 2 µg/kg, sodium thiopental 6 mg/kg, and atracurium 0.5 mg/kg. After intubation, maintenance of anesthesia was kept with one MAC of Isoflurane, along with the inspiratory gas mixture (50% oxygen and 50% N_2O). The patients were mechanically ventilated during surgery.

All intravenous fluids were warmed to 37°C before transfusion by inline fluid warmer. Apart from routine intraoperative monitoring (electrocardiogram (ECG), non-invasive blood pressure (NIBP), oxygen saturation (SpO_2), end-tidal carbon dioxide ($EtCO_2$), temperature monitoring was done via tympanic thermometer. All patients were covered by standard sterile drapes and OR temperature was maintained at 24 ± 2°C. Additional measures (warming mattress and warm air blankets) were taken if patients' temperature dropped below 35°C. "Study drug" was given 5 minutes before eye dressing. At the end of surgery, isoflurane and nitrous oxide were switched off and residual neuromuscular block was reversed with a mixture of atropine 0.02 mg/kg and neostigmine 0.04 mg /kg and trachea were extubated. Patients were covered with blanket and transferred to post-anaesthesia care unit (PACU)(ambient temperature of 24 ± 2°C) where they received supplemental oxygen 6 L/min and monitored for SpO_2 and hemodynamic variables (ECG, NIBP). In addition, patients were observed for occurrence and severity [Table 1] of postoperative shivering, at six different time intervals (on leaving or on arrival in PACU, at 15, 30, and 45 min of arrival in PACU and on discharge from PACU). Observations were recorded on the predesigned data collection form. Additional boluses of IV Pethidine 0.5 mg/kg, (maximum 30 mg/kg) were given to patients with shivering grade ≥2. Patients were discharged according to PACU discharge protocol.

Aesthetic time was defined from the start of induction to the time when the anesthetic, including nitrous oxide, was discontinued. The subsequent period until the patient responded to verbal command was recorded as the recovery time. If the systolic blood pressure were dropped to 20% less than baseline values, ringer-lactate serum and if necessary 10 mg of ephedrine was administered.

The severity of shivering was evaluated by a four-grade scale *by* another physician who was not aware of the drugs used. The grading was as follows: 0, no shivering; 1, no muscle contraction but mild fasciculation's of face or neck or peripheral vasoconstriction; 2, visible tremor involving one muscle group; 3, visible tremor involving more than one muscle group; and 4, gross muscular activity involving the entire body (16). In cases with grade 3-4 shivering for more than 4 min duration, the prophylaxis was considered ineffective and intravenous Pethidine 25 mg was administered.

Also, drug side effects and duration of extubation were evaluated and recorded. Patients were discharged from recovery based on modified Aldrete Score criteria (17).

Any side effects of the studied drug, including nausea, vomiting, constipation, light headedness, dizziness, drowsiness, headache, seizure, fever, diarrhea, rash, and itching, were recorded.

Post aesthetic sedation was checked every 20 min over 40 min in the PACU and graded, using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Score (18), as 0 = does not respond to pain, 1 = does not respond to mild prodding or shaking, 2 = responds only after mild prodding or shaking, 3 = responds only after name is called loudly and/or repeatedly, 4 = lethargic response to name spoken in normal tone, 5 = responds readily to name spoken. Recovery room temperature was kept between 22-23 ℃.

RESULTS

128 patients completed the study and 7 patients were excluded whom we explained in consort flow chart. All the study groups were comparable with respect to age, gender, BMI, and ASA status; however, there was male predominance in all the groups. All other intraoperative variables

(duration of patient stay in OR, duration of anesthesia, and temperature at start and end of procedure) including hemodynamic parameters were comparable and statistically insignificant [Table 1].

The number of patients who shivered during the observation period was significantly lower in the Alfentanil and Pethidine groups than that in the control group (Table 2). The number of patients who received extra Pethidine was significantly higher in the Alfentanil and Saline groups (Table 2). The distribution of the number of patients who began to shiver during various time periods was significantly different between three groups (Table 2). There was no significant difference in core temperature between the all groups. In terms of the incidence of postoperative shivering, in the Alfentanil group, seven patients (16.27 %) had shivering in the recovery process. This rate compared with the incidence of postoperative shivering in 11 patients (25.58 %) of control group and four patients (9.52 %) of Pethidine group shows a significant difference (P = 0.001) [Table 2]. During the operation, one of the patients in control group and the other in Pethidine group was injected with 10 mg ephedrine because of hypotension.

The intensity of shivering in three groups in recovery room has been shown in [Table 3].

Table 1. Demographic and operative details of patients in three groups.

	Alfantanil Group (N=43)	Pethidine Group (N=42)	Normal Saline (Placebo) Group (N=43)	P value
Age (y)	69.2±4.5	71.2±5.3	70.8±3.8	0.91
Height (cm)	162.3± 7.6	165.7± 5.4	170.1± 4.9	0.82
Weight (kg)	56.9±5.8	61.3±7.6	59.5±5.2	0.98
Male/Female	28/15	29/13	31/12	0.67
ASA II	32	27	30	0.81
ASA III	11	15	13	0.96
Duration of patient stay in OR(min)	91.3± 6.6	107.6± 7.1	109.9± 8.9	0.64
Temperature at start of procedure	37.1±0.4	37.2±0.6	36.8±0.3	0.88
Temperature at the end of procedure	37.3±0.3	37.1±0.4	37.4±0.61	0.94
Duration of Anesthesia (min)	65±8.5	59±6	61±7	0.93
Duration of recovery (min)	76±12	82±18	79±6	0.92

Data are expressed as mean ± standard deviation

Table 2: Number of shivering patients over time after emergence from anesthesia

	Alfantanil Group (N=43)	Pethidine Group (N=42)	Normal Saline (Placebo) Group (N=43)	P value
Begin shivering on arrival to PACU	0	0	1	0.001
Begin shivering at 15 of arrival to PACU	1	1	2	0.001
Begin shivering at 30 of arrival to PACU	4	2	3	0.004
Begin shivering at 45 of arrival to PACU	1	1	4	0.001
Begin shivering at 60 of arrival to PACU	1	0	1	0.046
Begin shivering on discharge from PACU	0	0	0	1
Total number of shivering patients	7	4	11	0.001
No of patients who received extra pethidine to treat shivering in PACU	2	0	3	0.001

Table 3: Intensity of shivering in three groups in recovery room has been shown in Table 3.

Shivering grading	Alfantanil Group (N=43)	Pethidine Group (N=42)	Normal Saline (Placebo) Group (N=43)	Total(%)
0	36(83.72%)	38(90.47%)	32(74.41)	106(82.81)
1	1(2.32%)	1(2.38%)	2(4.64%)	4(3.12)
2	3(6.96%)	2(4.76%)	3(6.96%)	8(6.24)
3	2(4.64%)	1(2.38%)	4(9.28%)	7(5.46)
4	1(2.32%)	0(0%)	2(4.64%)	3(2.34)
Total	43(100)	42(100)	43(100)	128(100)

DISCUSSION:

The results from our study showed that Alfentanil can be an effective drug to decrease the incidence of shivering and recovery time after anesthesia for Cataract surgeries but not as effective as pethidine. In one study, IV administration of Alfentanil 30 minutes before operation was assessed, their results showed that incidence of post anesthesia shivering was decreased but there was an increase in emergence time after operation (19 and 20). In another survey IV administration of Alfentanil had better preventive effects on post anesthesia shivering than Remifentanil (21). We could not find any study related to the effect of Alfentanil on postoperative shivering in patients with cataract surgery under Isoflurane anesthesia and we suggest that our study is a unique survey about this matter which showed that Alfentanil in patients can control the incidence of post-operative shivering .Alfentanil was found to decrease the recovery time after operation in patients. So, from our results we deducted that effect of Alfentanil on post anesthesia recovery time in patients is better than Pethidine. Some studies have shown that Pethidine does not delay recovery time after anesthesia, but in other ones pethidine can delay arousal from anesthesia and extend the time of discharge from operating room (24, 25). Through our investigation we could not find any related article about Alfentanil effects on recovery time after anesthesia so; we suppose that our study upon the effectiveness of Alfentanil on recovery time after anesthesia in patients is a unique study on this matter. We could not have equal sexes of patients and the male ones were dominant in the study. So, it seems that we cannot generalize our results to both sexes. The other limitation was that we did not have any lab data about the level of opium in patients' serum or urine and we relied on the history of patients about their addiction. It was due to an attempt to preserve patients' rights and we did not intend to create any discomfort for patients to have any test about their addiction. In summary, the IV of Alfentanil can be effective to decrease the incidence of shivering after operation in patients and to decrease recovery time after anesthesia but its effect in addicted patients needs more investigations.. In this study which done on patients undergoing elective cataract surgery under general anesthesia, the drugs of Pethidine, Alfentanil, and placebo were used and their effects on the prevention and control of postoperative shivering were evaluated. Although mechanism of Pethidine and Alfentanil is not completely understood, it probably acts directly on the thermoregulatory center or via opioid receptors

The shivering incidence rate in the control group was 25.58%. While in the Alfentanil group this rate was reduced to 16.27% and in the Pethidine group to 9.52%. Therefore, it can be concluded that the use of Pethidine and Alfentanil before the end of surgery, compared with the control group, significantly reduces the incidence of shivering. In addition, the use of Alfentanil can also reduce the incidence of shivering, but less than Pethidine. Statistically, there was a significant difference between the groups of Alfentanil and Pethidine.

In a study in 1997, it was concluded that administering 250 micrograms of Alfentanil

before the end of anesthesia cannot significantly reduce the incidence of shivering , but in another study in 1998, performed on ten volunteers (27) it became clear that neither Meperidine nor Alfentanil reduced the gain of shivering, as determined by either oxygen consumption or electromyography and opioid administration also failed to significantly decrease the maximum intensity of shivering but Meperidine and Alfentanil do not reduce the gain or maximum intensity of shivering (26, 27,28 and29).

Many studies have confirmed the effectiveness of Pethidine in preventing postoperative shivering (23 - 28). The anti-shivering mechanism of Pethidine is due to its action via *k* receptor rather than μ opioid receptors (29). However, Pethidine has some adverse effects which limit its use in some cases , it may cause respiratory depression especially in patients with previous history of opioids and anesthetics administration, the other side effects are hypotension, postoperative nausea and vomiting(30 -32). Therefore, it seems that proper alternatives should be determined for cases with contraindications for Pethidine administration. In the present study, using low doses of Alfentanil, similar results were obtained. This fact confirms that using the dose of 500 micrograms of Alfentanil could reduce the shivering incidence, in the meantime it could prevent from its side effects at higher doses.

Compared with placebo, Alfentanil reduced the incidence of postoperative shivering (16.27% compared with 25.58 %) ($P < 0.001$).

In conclusion, this study showed that administering low dose of Alfentanil before the end of anesthesia was effective and reduced shivering during the recovery but not as good as Pethidine. Despite this fact, in the present study the effect of Alfentanil in reducing postoperative shivering has been much better than control group but not as Pethidine. Perhaps, cause of this issue may be the short duration of action of this drug or low dose of that which needs further investigations. Although the amounts of Pethidine and Alfentanil administered in the prevention or treatment of postoperative shivering rarely has a significant cardiovascular effect, these drugs and other narcotic drugs have potentially high risk of respiratory disorders in patients, especially if they are administered during surgery (33 , 34)

There are a few limitations to this investigation. First, the optimal dose of Alfentanil required to prevent postoperative shivering has not been established. A dose of 500 micrograms was selected for the current investigation based on data that this maybe the optimal effective dose in the prevention of postoperative shivering (13, 14, 15, 19, 20 and 27). Future dose-response studies will be required to establish the most appropriate dosing regimen of Alfentanil for optimal prevention of postoperative shivering. Second, we observed no complications directly attributable to Alfentanil. However, our study was likely underpowered to detect uncommon adverse clinical outcomes potentially related to Alfentanil. Finally, our study limited to recovery period so this study could not compare the long-term effects of groups and length of stay in hospital between three groups.

CONCLUSION

The prophylactic use of Alfentanil in a dose of 500 micrograms administered at the end of surgery when Isoflurane is used as an maintenance agent significantly reduces the episodes of postoperative shivering requiring treatment but not as good as Pethidine. Another advantage of Alfentanil is the reduced recovery duration time and also requirement of postoperative Pethidine in these patients in the recovery room for treatment of shivering.

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Footnotes

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REFERENCES:

1. Heidari SM, Rahimi M, Soltani H, Hashemi SJ, Shabahang S. Premedication with oral tramadol reduces severity of postoperative shivering after general anesthesia. A dv Biomed Res 2014; 27:3-64.
2. Tewari A, Dhawan I, Mahendru V, Katyal S, Singh A, Narula N. A comparative study evaluating the prophylactic efficacy of oral clonidine and tramadol for perioperative shivering in geriatric patients undergoing transurethral resection of prostate. J Anaesthesiol Clin Pharmacol 2014; 30(3):340-4.
3. Dabir S, Jahandideh M, Abbasinazari M, Kouzekanani H, Parsa T, Radpay B. The efficacy of a single dose of pethidine, fentanyl and morphine in treating postanesthesia shivering.Pak J Pharm Sci 2011;24(4):513-7.
4. Lenhardt R. The effect of anesthesia on body temperature control. Front Biosci (Schol Ed). 2010 ; 1:1145-54.
5. Entezariasl M, Isazadehfar K. Dexamethasone for prevention of postoperative shivering: a randomized double-blind comparison with pethidine. Int J Prev Med 2013 ;4
6. Kim YA, Kweon TD, Kim M, Lee HI, Lee YJ, Lee KY. Comparison of meperidine and nefopam for prevention of shivering during spinal anesthesia. Korean J Anesthesiol. 2013;64(3):229-33.
7. Chiang MH, Chung KC, Syue YJ, Chia-Shen Yang J, Chien CY, Kuo YR. The role of meperidine in reduction of postanesthetic shivering and its possible impact on flap outcomes. Microsurgery. 2014;34(2):106-11.
8. Dai YH, Ou KL, Chu PW. Cerebellar and oculomotor dysfunction induced by rapid infusion of pethidine. BMJ Case Rep. 2014 ; 11;2-14.
9. Darvish H, Memar Ardestani B, Mohammadkhani Shali S, Tajik A. Analgesic Efficacy of Diclofenac and Paracetamol vs. Meperidine in Cesarean Section.Anesth Pain Med. 2013 ; 26:4(1)
10. Banihashem N, Hasannasab B, Alereza H. Does dexamethasone prevent subarachnoid meperidin-induced nausea, vomiting and pruritus after cesarean delivery? Saudi J Anaesth. 2013;7(2):138-41.
11. Dai YH, Ou KL, Chu PW. Cerebellar and oculomotor dysfunction induced by rapid infusion of pethidine. BMJ Case Rep. 2014 Mar 11;2014.
12. Dai YH, Ou KL, Chu PW. Cerebellar and oculomotor dysfunction induced by rapid infusion of pethidine.BMJ Case Rep. 2014 Mar 11;2014.
13. Alfonsi P, Passard A, Gaude-Joindreau V, Guignard B, Sessler DI, Chauvin M. Nefopam and alfentanil additively reduce the shivering threshold in humans whereas nefopam and clonidine do not. Anesthesiology. 2009 Jul;111(1):102-9.
14. Sessler DI. Treatment: meperidine, clonidine, doxapram, ketanserin, or alfentanil abolishes short-term postoperative shivering.Can J Anaesth. 2003;50(7):635-7.
15. Asmussen H, Jørgensen L. Remifentanil and eye surgery. A randomized, clinical comparison of propofol/remifentanil anesthesia and propofol/fentanyl/alfentanil anesthesia].Ugeskr Laeger. 2003 ; 21:165(17):1774-8.
16. Badjatia N, Strongilis E, Gordon E, Prescutti M, Fernandez L, Fernandez A, Buitrago M, Schmidt JM, Ostapkovich ND, Mayer SA. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. Stroke. 2008;39(12):3242-7.
17. Eberhart LH, Gerlach H, Knaber R, Koch T, Morin AM, Röhr F, Wagner S, Wulf H, Zoremba M. Implementation of new standards in anaesthesia. Exemplified by the ad hoc introduction of desflurane in 10 German hospitals. Anaesthesist. 2011;60(1):39-48.

18. Berry BD, Ekman EF, Muckerman RC 2nd, Shore N, Hardi R. Safety evaluation of fospropofol for sedation during minor surgical procedures. J Clin Anesth. 2010;22(4):260-7.
19. Alfonsi P, Passard A, Gaude-Joindreau V, Guignard B, Sessler DI, Chauvin M. Nefopam and alfentanil additively reduce the shivering threshold in humans whereas nefopam and clonidine do not. Anesthesiology. 2009 Jul;111(1):102-9.
20. Crozier TA, Kietzmann D, Döbereiner B. Mood change after anaesthesia with remifentanil or alfentanil. Eur J Anaesthesiol. 2004;21(1):20-4.
21. Komatsu R, Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC. Remifentanil for general anaesthesia: a systematic review. Anaesthesia. 2007;62(12):1266-80.
22. Trevisani L, Cifalà V, Gilli G, Matarese V, Zelante A, Sartori S. Post-Anaesthetic Discharge Scoring System to assess patient recovery and discharge after colonoscopy. World J Gastrointest Endosc. 2013;5(10):502-7.
23. Cinar K, Yakut M, Ozden A. Sedation with midazolam versus midazolam plus meperidine for routine colonoscopy: a prospective, randomized, controlled study. Turk J Gastroenterol. 2009;20(4):271-5.
24. Hayee B, Rowbotham D, Saxena V, McNair A.Fentanyl vs. pethidine as sedation for gastrointestinal endoscopy. Aliment Pharmacol Ther. 2009;30(3):312-3.
25. Fanti L, Agostoni M, Gemma M, Gambino G, Facciorusso A, Guslandi M, Torri G, Testoni PA. Remifentanil vs. meperidine for patient-controlled analgesia during colonoscopy: a randomized double-blind trial. Am J Gastroenterol. 2009;104(5):1119-24.
26. Ikeda T, Sessler DI, Tayefeh F, Negishi C, Turakhia M, Marder D, Bjorksten AR, Larson MD. Meperidine and alfentanil do not reduce the gain or maximum intensity of shivering. Anesthesiology. 1998;88(4):858-65.
27. Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering.Br J Anaesth. 1997;79(4):541-2.
28. Kurz A, Ikeda T, Sessler DI, Larson MD, Bjorksten AR, Dechert M, Christensen R. Meperidine decreases the shivering threshold twice as much as the vasoconstriction threshold.Anesthesiology. 1997;86(5):1046-54.
29. Liu ZH, He Y, Jin WQ, Chen XJ, Zhang HP, Shen QX, Chi ZQ. Binding affinity to and dependence on some opioids in Sf9 insect cells expressing human mu-opioid receptor. Acta Pharmacol Sin. 2003;24(9):859-63.
30. Treeprasertsuk S, Rerknimitr R, Angsuwatcharakon P, Ridtitid W, Thanapirom K, Kongkam P, Ponuthai Y, Viriyautsahakul V. The safety of propofol infusion compared to midazolam and meperidine intravenous bolus for patients undergoing double balloon enteroscopy.J Med Assoc Thai. 2014;97(5):483-9.
31. Eydi M, Golzari SE, Aghamohammadi D, Kolahdouzan K, Safari S, Ostadi Z. Postoperative Management of Shivering: A Comparison of Pethidine vs. Ketamine.Anesth Pain Med. 2014 14;4(2):e15499.
32. Darvish H, Memar Ardestani B, Mohammadkhani Shali S, Tajik A. Analgesic Efficacy of Diclofenac and Paracetamol vs. Meperidine in Cesarean Section.Anesth Pain Med. 2013;4(1): 9997.
33. Kim YA, Kweon TD, Kim M, Lee HI, Lee YJ, Lee KY. Comparison of meperidine and nefopam for prevention of shivering during spinal anesthesia.Korean J Anesthesiol. 2013;64(3):229-33.
34. Elbohoty AE, Abd-Elrazek H, Abd-El-Gawad M, Salama F, El-Shorbagy M, Abd-El-Maeboud KH. Intravenous infusion of paracetamol versus intravenous pethidine as an intrapartum analgesic in the first stage of labor.Int J Gynaecol Obstet. 2012;118(1):7-1