

Assessment of Psychomotor Recovery after Etomidate and Propofol Induction: A Randomized Double-Blind Trial

Jyoti Kale, Neha Panse*, Ketki Maske, Pranali Nighukar

Department of Anesthesiology, Department of Anaesthesiology, Smt. Kashibai Navale Medical College, Pune, Maharashtra, India.

ARTICLE INFO

Article history:

Received 04 March 2021

Revised 26 March 2021

Accepted 10 April 2021

Keywords:

Psychomotor;
Propofol;
Etomidate;
Myoclonus;
Recovery

ABSTRACT

Background: The very idea of faster recovery and early ambulation has prompted patients to opt for day care surgeries. The concept of ERAS (enhanced recovery after surgery) is the backbone to achieve this goal. We conducted this study with primary objective to compare the post-operative recovery with etomidate and propofol in terms of early recovery (awakening), intermediate recovery (psychomotor and cognitive recovery) and ambulation “home readiness” and secondary objective to study the adverse effects.

Methods: 60 eligible patients scheduled for day care gynaecological procedures were randomised in two groups of 30 each. Group E received etomidate 0.2mg/kg and group P received propofol 2mg/kg. Early, intermediate and late postoperative recovery (ambulation) was studied in both groups.

Results: Demography between the groups were comparable while hemodynamic fluctuations were more with propofol ($p > 0.05$), early recovery was faster with etomidate ($p = 0.07$), psychomotor tests revealed better alertness with etomidate ($p = 0.1$) and patient could ambulate earlier in etomidate group.

Conclusion: Both propofol and Etomidate facilitate early recovery but etomidate provides hemodynamic stability with early awakening, more alert patients and better ambulation and was found to be superior for day care surgeries.

In the present times of ERAS (Enhanced recovery after surgery) there is a need for anaesthetic agents that provide not only optimal operating conditions but also allow rapid recovery after surgery. Propofol and Etomidate are two such drugs which provide early awakening from anaesthesia and have been used for ambulatory anaesthesia.

Propofol due to its unique pharmacodynamics and pharmacokinetics allows rapid recovery from anaesthesia and has been widely used in day care surgeries [1-3]. However, the side effects of depression in respiratory and cardiovascular parameters by Propofol urges a need to look for an agent with better hemodynamic profile. An induction dose of propofol results in 25% to 30% incidence of apnoea and a 25% to 40% reduction in Mean arterial pressure [4].

While unlike propofol, etomidate causes lesser respiratory depression and minimal hemodynamic

fluctuations. Yet certain side effects of etomidate like myoclonus and post-operative nausea and vomiting limits its use. These side effects can be constrained by using etomidate in combination with benzodiazepines and antiemetics.

Psychomotor tests are good tools to assess the recovery from anaesthesia and have been widely studied with Propofol since ancient times but to the best of our knowledge there is no literature suggesting evidence of psychomotor studies with etomidate.

We conducted this trial with the primary aim of comparing the efficacy of two widely used drugs ‘propofol’ and ‘etomidate’ in facilitating early recovery from anaesthesia with a detailed monitoring of early and intermediate recovery, stressing on psychomotor and cognitive effects and ambulatory recovery from anaesthesia, particularly the time course of recovery

The authors declare no conflicts of interest.

*Corresponding author.

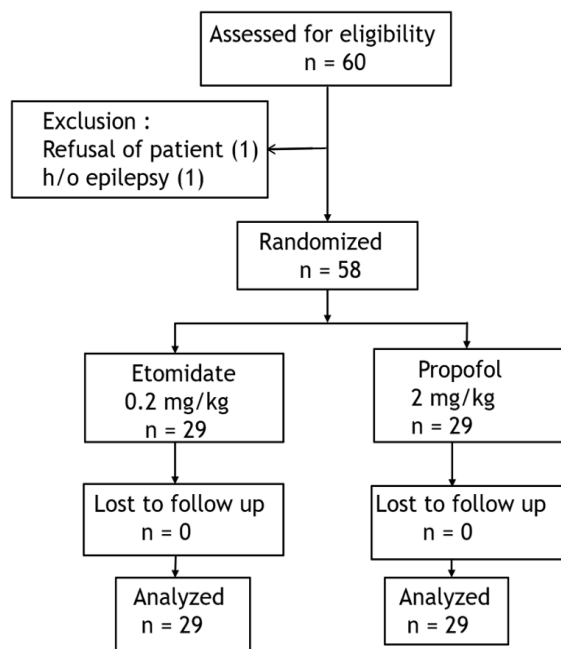
E-mail address: drnehaghule@gmail.com

events and the secondary aim was to study the side effects if any.

Methods

We designed this prospective randomized double-blind trial to be conducted from Jan 2019 to Dec 2019 in complete accordance with the guidelines of Helsinki. After obtaining the institutional ethical committee approval (SKNMC/Ethics/App/2018/472) and written informed consent, 60 patients of American society of anaesthesiologist's physical status I and II in the age group of 18-60 years, posted for day care surgery e.g. MTP, laparoscopic tubal ligation, diagnostic Hyster laparoscopy, dilatation and curettage, hysteroscopy were enrolled for the study. Patients not willing to participate in the study, h/o epilepsy, use of drugs affecting the central nervous system, chronic sedative or opioid analgesic use, adrenocortical insufficiency or h/o general anaesthesia in the past 7 days were not included in the study.

Figure 1- Consort flow chart



They were randomly allocated into two groups by drawing of consecutively numbered envelopes containing the labels propofol or etomidate. Group E received inj etomidate 0.2mg/kg while Group P received inj propofol 2mg/kg. The anaesthesiologist observing the preoperative and postoperative psychomotor tests, the anaesthesiologist administering anaesthesia and the patients were blinded to type of induction agent till the end of trial. On the morning of surgery, baseline measurements of the following psychomotor tests: (1) aiming test (2) trieger dot test

(3) shape deletion test (4) address recall test were obtained in the pre-operative room.

1. Aiming test: Two hundred 5-mm diameter circles linked in lines of 20 each, across a sheet of paper, were presented to patients and asked to place dot inside each circle within 90 seconds. The numbers of dots correctly placed within circles were recorded. This assessed hand-eye co-ordination

2. Trieger dot test: It assessed hand eye coordination and was a simple paper pencil test requiring patients to connect 21 dots in the form of letter "S" with a micro tip pen. Scoring was done by calculating number of dots missed.

3. Shape deletion test: This test assessed the cognition. One minute to delete as many circles as possible out of mixed shapes provided. Correct deletions, the errors and incorrect deletions or omissions were scored [5].

4. Address recall test: Patient is asked to recall his address to assess postoperative cognition function.

5. Romberg's test: The patient is asked to stand and close their eyes. An increased loss of balance is interpreted as a positive Romberg's test. The Romberg test is a test of the body's sense of positioning (proprioception), which requires healthy functioning of the dorsal columns of the spinal cord. Romberg's test was performed to assess post-operative recovery.

After receiving patient in the operating room (OR) all the standard monitors including electrocardiogram, non-invasive blood pressure and oxygen saturation were attached and baseline vital parameters were recorded. A ringer lactate infusion was started. The patients were premedicated with inj. Ondansetron 0.1mg/kg, inj. Midazolam 0.03mg/kg and inj. Glycopyrrolate 4mcg/kg. The patients were induced according to the study group allocated.

Induction time is defined as the time from the start of injection to the loss of eyelash reflex. Induction parameters were recorded, Classic LMA was inserted and anaesthesia was maintained with 40:60 ratios of oxygen and nitrous oxide with sevoflurane. The systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rates were recorded at induction, LMA insertion, surgical incision and then every five minutes until the completion of surgery and after LMA removal. After the LMA removal, on OT table the patient's response to oral commands and the recovery was studied as follows:

Preoperative reading was taken as the baseline and the test was repeated post operatively every 15 minutes until 90 minutes before the patient was shifted to ward.

1. Waking time: the duration from the end of anaesthesia until the patient is able to respond to oral commands.

2. Talking time: the duration from the end of anaesthesia till the patient is able to talk.

3. Sitting time: the duration from the end of anaesthesia till the patient is able to sit without support.

4. Standing time: the duration from the end of anaesthesia till the patient is able to stand without support.

In the recovery room, as soon as the patient was oriented and capable of sitting independently, psychometric aiming test, trieger dot, shape deletion test and address recall tests (defined earlier) were performed. The patients were also observed for urine output and subjective complaints of sleepiness, headache and PONV up to 4 hrs of recovery.

Using STATA software 14.0 (STATA corporation, College station, TX, USA) a minimum of 28 patients were required to achieve a significance level of 95 % in recovery within a power of 80% and type I error of 0.05. We included 60 patients with 30 in each group considering any dropouts.

Statistical data analysis was done by appropriate statistical method with statistical software SPSS ver. 20. All the data is presented as proportions or as mean values \pm standard deviation. Statistical analysis of haemodynamic parameters and mean of induction and recovery times was performed by unpaired 2-tailed t tests. Psychometric aiming test, trigger dot, shape deletion and address recall tests were analysed using paired and unpaired t tests. Differences in proportions were analysed by chi-square test with continuity correction. Statistical significance was accepted for $p < 0.05$.

Results

58 patients completed the study. 2 were excluded from the study, as one refused to participate and the other was a known case of epilepsy.

Demographic data are presented in (Table 1). Both groups were comparable with respect to age, weight, ASA grades, duration and type of surgical procedure.

Table 1- Represents demographic data.

| | Etomidate (n= 29) | Propofol (n= 29) |
|-------------------|------------------------------|-----------------------------|
| Age (years) | 32.6 \pm 7.0 | 36.7 \pm 9.0 |
| Weight (kg) | 63.3 \pm 15.4 | 63.0 \pm 13.2 |
| ASA status (I/II) | 28/1 | 23/6 |

All patients in both groups lost consciousness with the administered induction dose and the Time to loss of eyelid reflex was lesser for Group E- (36.3 \pm 8.0 secs) versus (42.6 \pm 9.6 secs) in Group P. (Table 2) Two patients in Group E exhibited involuntary movements during the induction of anaesthesia. Pain on injection was noted in 3 subjects one from Group E and two from Group P.

Table 2- Represents Induction dosage and Induction time

| | Etomidate (n = 29) | Propofol (n = 29) |
|-----------------------------|-------------------------------|------------------------------|
| Induction dose (mg/kg) | 0.2 \pm 0.1 | 2.18 \pm 0.37 |
| Cessation of counting (sec) | 29.8 \pm 6.1 | 42.2 \pm 27.1 |
| Loss of lid reflex (sec) | 36.3 \pm 8.0 | 42.6 \pm 9.6 |
| Duration of anaesthesia | 24.1 \pm 12.0 | 25.3 \pm 16.5 |

(Figure 2 and 3) illustrate the haemodynamic changes during the induction and maintenance of anaesthesia. Peak heart rates and blood pressures were observed, in all cases during LMA insertion in both groups but the rise was significantly less in patients of Group E. Mean intraoperative heart rates were also significantly lower with Group E at 5 and 10 minutes and after removing LMA.

Figure 2- Represents Heart Rate (beats/min)

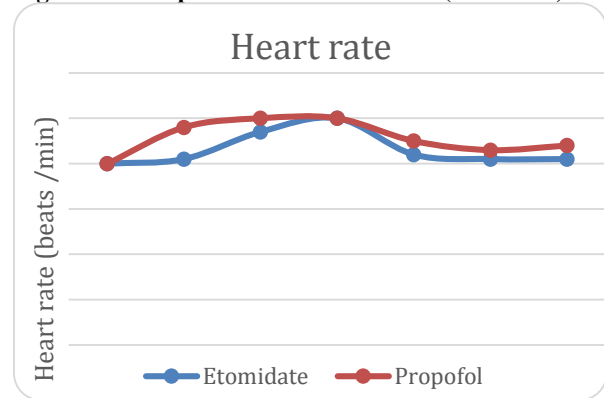
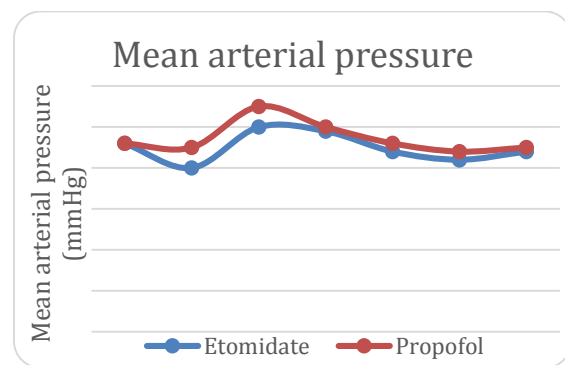


Figure 3- Represents mean arterial pressure



Patients of Group P took longer time to open eyes (6.4 \pm 4.3 mins) versus (4.9 \pm 2.4 mins) than group E and also to obey commands (7.2 \pm 2.7 mins) versus (6.0 \pm 2.5 mins) of Group E after surgery. Patients of Group E recalled address in (14.0 \pm 6.2 mins) which took (18.2 \pm 11.3 mins) for Group P. Patients of Group E were able to sit with minimal support as early as (36.9 \pm 12.6 mins) as compared to Group P (44.9 \pm 22.8 mins).

Psychomotor recovery was significantly faster and consistent with Group E as compared to Group P in all

3 psychomotor tests. (Figure 4, 5 and 6) Patients in Group P remained impaired until 2 hrs ($p < 0.01$) as compared to Group E which recovered to baseline by 1 hr for aiming, trieger dot, shape deletion and address recall tests.

Figure 4- Represents results of Aiming Test

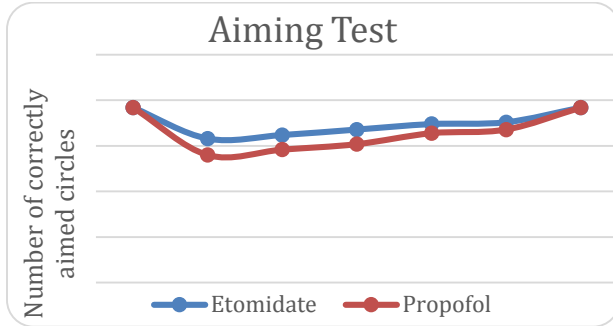


Figure 5- Represents results of Trieger dot test

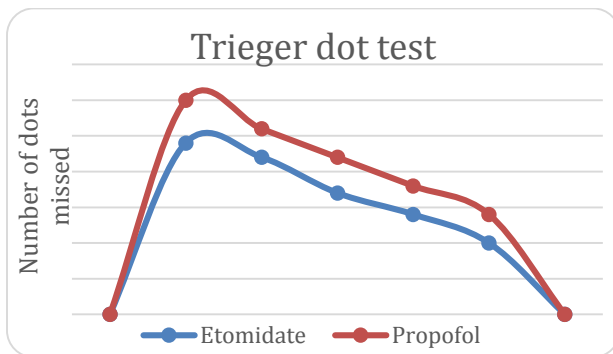
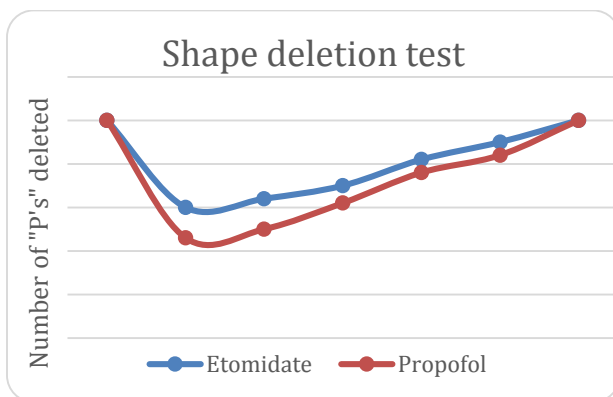


Figure 6- Represents results of Shape deletion test



Time to eye opening, orientation and response to verbal command were compared in both groups and (Table 3) and found that dizziness sufficient to prevent standing in the immediate postoperative period was noted in 33% of the patients of group P versus 13 % of group E. A higher incidence of nausea and vomiting with Group E was noted which was not statistically significant. Intraoperative awareness occurred in one subject given etomidate. Patients in the Group E achieved an Aldrete score of 10, at (26.1 ± 7.3 mins)

whereas Group P achieved at (33.2 ± 22.6 mins). 7 patients from Group E and 13 from Group P were unable to stand even after 90 minutes. Of the remaining subjects, 4 in the propofol group had a negative Romberg's test but could not walk.

Table 3- Represents time taken for Recovery

| | Etomidate (n = 29) | Propofol (n = 29) | P value |
|--|-----------------------|----------------------|------------|
| Eye opening (min) | 4.9 ± 2.4 | 6.4 ± 4.3 | 0.10 |
| Response to verbal command (min) | 6.0 ± 2.5 | 7.2 ± 2.7 | 0.07 |
| Address recall (min) | 14.0 ± 6.2 | 18.2 ± 11.3 | 0.08 |
| Aldrete score 10 (min) | 26.1 ± 7.3 | 33.2 ± 22.6 | 0.1 |
| Sit independently (min) | 36.9 ± 12.6 | 44.9 ± 22.8 | 0.09 |
| Ability to walk at discharge (no. Of patients) | 22 | 16 | - |

Discussion

Enhanced recovery after surgery (ERAS) is a protocolized scientific pathway applied to boost the outcome and enhance the recovery phase after surgery. This includes multimodal evidence-based strategies at every step of perioperative care including the rehabilitation phase. The background milieu/requisites include patient education and a dedicated team approach for implementing these protocols [6]. The concept of ERAS protocol was first pioneered by Prof. Kehlet and Wilmore somewhere in the last decade of the twentieth century [7].

There is little evidence to favour one anaesthetic technique over another but the general principles of enhanced recovery, support the use of medications which have minimal postoperative hangover and minimal effects on gastric motility [8]. Thus, total intravenous anaesthesia with short acting agents is preferred. Early mobilization aims to reduce skeletal muscle loss and improve respiratory function and oxygen delivery to tissues which in turn optimises recovery [9]. Patients should be encouraged to achieve daily procedure specific goals, which can be guided by various proformas to ensure all areas of care to receive attention. Ideally, patients should sit out of bed for 2 h on the day of surgery and 6 h a day until discharge [10].

Propofol (2, 6diisopropyl phenol), an intravenous hypnotic agent, undergoes rapid redistribution, metabolism to inactive metabolites, and has a short elimination half-life. These pharmacokinetic characteristics make this a suitable agent for outpatient anaesthesia by allowing rapid recovery of psychomotor and cognitive function.

Etomidate is R-1-(1-ethylphenyl) imidazole-5-ethyl ester intravenous hypnotic agent that acts directly on GABA receptor complex blocking neuroexcitation producing sedation, hypnosis and anaesthesia without analgesia. Etomidate is a preferred drug in hemodynamically unstable patients. It has rapid onset, short duration of action, rapid distribution and very short elimination half-life. In this study, which employed general anaesthesia, propofol was compared with equipotent dose of etomidate for procedures of short duration (both agents favour ERAS protocol). Ours was a double-blind study and the blinding was favoured by similar appearance of both drugs.

Earlier studies have compared etomidate and propofol for general anaesthesia for induction properties but to the best of our knowledge none have studied the psychomotor recovery after etomidate induction.

Supriya Aggarwal and colleagues conducted a comparative study between propofol and etomidate in patients under general anaesthesia and vital parameters at induction, laryngoscopy and thereafter were recorded for comparison [11]. Adverse effects viz. pain on injection, apnoea and myoclonus were carefully watched and concluded that etomidate is a better agent for induction than propofol in view of hemodynamic stability and less pain on injection. In our study the number of subjects requiring analgesics and antiemetics was comparable between groups and hence it had no effect on the psychomotor and cognitive function test results when comparing the two groups. Inductions were both rapid and smooth with propofol but pain or discomfort on injection was more common with propofol but was never severe enough to necessitate the discontinuation of injection with etomidate. A previous study by Briggs showed that the incidence of pain is diminished when the intravenous catheter is placed in a large vein [12]. The cardiorespiratory effects of propofol have been compared with other intravenous agents in several studies. The hypotension related to propofol is caused by sympathetic inhibition and disturbances in baroreflex mechanisms; however, etomidate preserves haemodynamic stability by stabilizing sympathetic responses and preserving autonomic reflexes [13]. Wu et al [14] also concluded that etomidate preserves hemodynamic stability during anaesthesia. In our study we found that the tachycardia response to laryngoscopy, intubation and surgical stimulation was more with propofol. The only significant difference in blood pressure between the two groups was a diminished rise of both systolic and diastolic pressure

post-intubation seen with propofol. Prys-roberts [15] and Grounds [16] have both suggested that propofol resets the baroreceptor response to blood pressure changes.

Like others, we found recovery times of all measured variables were similar with both drugs. Patient opened their eyes and responded to verbal command earlier in etomidate group. Orientation to name, place and date of birth was also attained early in etomidate group. Psychomotor and cognitive testing was performed every 15 min until patient was shifted out of recovery room but only after the patient was able to sit up independently. The ability to delete shape, trieger test and aiming test had returned to baseline, in both groups, prior to transfer to the ward and patients were able to recall address.

Salimetoklua and team compared etomidate–remifentanyl and propofol–remifentanyl sedation in patients scheduled for colonoscopy and concluded that the remifentanyl combination with etomidate provides fewer haemodynamic and respiratory complications than the combination with propofol but is more frequently associated with myoclonus and postoperative nausea and vomiting and also the recovery time and emergence from anaesthesia are shorter with etomidate–remifentanyl than with propofol–remifentanyl [17].

S Pawar, A Malde studied the time course of psychomotor, cognitive and ambulatory recovery after propofol day care anaesthesia and stated that the patients with propofol showed faster recovery than thiopentone and were better oriented [18]. As per our hospital protocol, all patients stay a minimum of 90 mins in our postoperative recovery room prior to shift out to general ward. We found that the early cognitive and psychomotor function recovery with the use of both etomidate and propofol is of clinical importance as it facilitates ERAS. The majority of subjects in both groups were satisfied with their anaesthesia.

There are certain limitations of the study, firstly the psychomotor studies have not been studied with etomidate earlier and more studies with a larger sample size should be conducted to derive a conclusion, and secondly the results of the tests are totally dependent on patient's cooperation and discretion postoperatively which needs to be considered and the practice factor for psychomotor tests could not be eliminated. Also we didn't include ASA III and above patients and so we could not assess the safety of etomidate in high risk cases.

Conclusion

To conclude both etomidate and propofol, facilitated early recovery from anaesthesia but etomidate was found to be superior in terms of hemodynamic stability, recovered alertness, cognitive function and early ambulation. Compared with propofol, etomidate showed reduced apnoea or hypoxemia, and injection pain, but

with an increased myoclonus which can be easily controlled by combination with fentanyl and midazolam.

References

- [1] Korttila K, Nuotto EJ, Lichtor JL, Ostman PL, Apfelbaum J, Rupani G. Clinical recovery and psychomotor function after brief anesthesia with propofol or thiopental. *Anesthesiology*. 1992; 76(5):676-81.
- [2] Korttila K. Recovery from propofol: does it really make a difference? *J Clin Anesth*. 1993; 5(6):443-6.
- [3] Korttila K, Ostman P, Faure E, Apfelbaum JL, Prunskis J, Ekdawi M, et al. Randomized comparison of recovery after propofol-nitrous oxide versus thiopentone-isoflurane-nitrous oxide anaesthesia in patients undergoing ambulatory surgery. *Acta Anaesthesiol Scand*. 1990; 34(5):400-3.
- [4] Meng QT, Cao C, Liu HM, Xia ZY, Li W, Tang LH, et al. Safety and efficacy of etomidate and propofol anesthesia in elderly patients undergoing gastroscopy: A double-blind randomized clinical study. *Exp Ther Med*. 2016; 12(3):1515-24.
- [5] Mayer M, Doenicke A, Nebauer AE, Hepting L. Propofol und Etomidat-Lipuro zur Einleitung einer Allgemeinanästhesie. Häodynamik, Venenverträglichkeit, subjektives Empfinden und postoperative Übelkeit [Propofol and etomidate-Lipuro for induction of general anesthesia. Hemodynamics, vascular compatibility, subjective findings and postoperative nausea]. *Anaesthesist*. 1996; 45(11):1082-4.
- [6] Kahokehr A, Sammour T, Zargar-Shoshtari K, Thompson L, Hill AG. Implementation of ERAS and how to overcome the barriers. *Int J Surg*. 2009; 7(1):16-9.
- [7] Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg*. 2002; 183(6):630-41.
- [8] White PF, Kehlet H, Neal JM, Schrickler T, Carr DB, Carli F; Fast-Track Surgery Study Group. The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. *Anesth Analg*. 2007;104(6):1380-96.
- [9] Pappaspyros S, Uppal S, Khan SA, Paul S, O'Regan DJ. Analysis of bedside entertainment services' effect on post cardiac surgery physical activity: a prospective, randomised clinical trial. *Eur J Cardiothorac Surg*. 2008; 34(5):1022-6.
- [10] Massey RL. A randomized trial of rocking-chair motion on the effect of postoperative ileus duration in patients with cancer recovering from abdominal surgery. *Appl Nurs Res*. 2010; 23(2):59-64.
- [11] Aggarwal S, Goyal VK, Chaturvedi SK, Mathur V, Baj B, Kumar A. Estudo comparativo entre propofol e etomidato em pacientes sob anestesia geral [A comparative study between propofol and etomidate in patients under general anesthesia]. *Rev Bras Anestesiol*. 2016; 66(3):237-41.
- [12] Briggs LP, Clarke RS, Dundee JW, Moore J, Bahar M, Wright PJ. Use of di-isopropyl phenol as main agent for short procedures. *Br J Anaesth*. 1981; 53(11):1197-202.
- [13] Ebert TJ, Muzi M, Berens R, Goff D, Kampine JP. Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. *Anesthesiology*. 1992; 76(5):725-33.
- [14] Wu J, Yao S, Wu Z, Wu Z, Chu S, Xia G, et al. A comparison of anesthetic regimens using etomidate and propofol in patients undergoing first-trimester abortions: double-blind, randomized clinical trial of safety and efficacy. *Contraception*. 2013; 87(1):55-62.
- [15] Prys-roberts c. Haemodynamic effects of 'diprivan' infusion anaesthesia; comparison with other intravenous and volatile anaesthetics. *Vii european congress of anaesthesiology abstracts iii*; 1986; 296.
- [16] Grounds RM, Twigley AJ, Carli F, Whitwam JG, Morgan M. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. *Anaesthesia*. 1985; 40(8):735-40.
- [17] Toklu S, Iyilikci L, Gonen C, Ciftci L, Gunenc F, Sahin E, et al. Comparison of etomidate-remifentanyl and propofol-remifentanyl sedation in patients scheduled for colonoscopy. *Eur J Anaesthesiol*. 2009; 26(5):370-6.
- [18] Pawar S, Malde A. Time course of psychomotor, cognitive and ambulatory recovery after propofol day case anesthesia: a randomized double blind study. *The internet journal of anesthesiology*. 2010; 23(1).