

## Comparison of the Effects of Thoracic Epidural Anesthesia with General Anesthesia on Hemodynamic Changes and its Complications in Patients Undergoing Laparoscopic Cholecystectomy

### Abstract

**Background:** Epidural anesthesia (EA) today has been used extensively in surgical procedures and the management of pain associated with midwifery and chronic pain. This type of anesthesia can be done in different technical, physiological, and pharmacological ways. The aim of this study was to compare the effects of thoracic EA with general anesthesia (GA) on hemodynamic changes and its complications in patients underwent laparoscopic colonoscopy. **Materials and Methods:** This clinical trial study was conducted on 80 patients undergoing laparoscopic cholecystectomy with EA or GA based on inclusion and exclusion criteria. The patients were randomly divided into two groups of 40 and changes in blood pressure, systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), and arterial blood oxygen saturation were measured. The incidence of nausea, vomiting, chills, and itching in the two groups was recorded. The analysis was performed descriptively and also using *t*-test and Chi-square tests. **Results:** The results showed that the mean of SBP and DBP, HR, and arterial blood oxygen saturation and the incidence of nausea and vomiting was statistically significant ( $P < 0.05$ ) between the two groups at 4, 6, and 12 h after anesthesia and it was higher in a group of GA. There was no significant difference in shivering and itching between the two groups ( $P > 0.05$ ). **Conclusion:** The results of this study indicated that thoracic EA in patients with laparoscopic cholecystectomy has significant effects on factors such as SBP and DBP and arterial blood oxygen saturation. Furthermore, EA has fewer complications than GA, and it is the preferable approach.

**Keywords:** Epidural anesthesia, general anesthesia, hemodynamic changes, laparoscopic cholecystectomy

### Introduction

Today, laparoscopy is considered as the golden standard for cholecystectomy surgery.<sup>[1]</sup> The presence of air in the peritoneum and the condition of the patient during laparoscopic surgery lead to a series of changes in pathophysiology that make it difficult to manage anesthesia.<sup>[2]</sup> Accordingly, our knowledge of anesthesia and the inappropriate choice of techniques can reduce the complications associated with surgery, and subsequently, the clinical prognosis of patients after surgery.<sup>[3]</sup> Anesthesiologist has several approaches, including general anesthesia (GA) and regional anesthesia such as epidural; however, GA is the most commonly used technique.<sup>[4]</sup> GA with tracheal intubation and control of ventilation is a safe and secure way in laparoscopic

operations that last for a long time,<sup>[5]</sup> but causes physiological fluctuations required rapid and serious interventions, with complications such as nausea, vomiting, sore throat, headache, shivering, and delayed return to normal mental function<sup>[6,7]</sup> and is not necessarily the best available choice and depending on the doctors' decision it may use regional anesthesia procedures such as epidural.<sup>[8]</sup> Today, epidural anesthesia (EA) is extensively used in surgery and pain control of obstetrics and chronic pain. Such type of anesthesia can be done in a variety of ways, which are technically, physiologically, and pharmacologically different with each other.

The epidural catheter provides the possibility of continuous and prolonged

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injection of local anesthetics or opioid solutions (or both) that is very useful for postoperative pain control.<sup>[9]</sup> Other benefits include fewer side effects such as nausea and vomiting,<sup>[10]</sup> relative staining in the femoral vein during laparoscopy,<sup>[11]</sup> suitability for patients with severe pulmonary dysfunction,<sup>[12]</sup> resulting in less disturbance in safety performance and less stay in the hospital.<sup>[13]</sup> Despite the above-mentioned benefits, EA requires a sophisticated, skillful surgical technique. If the patient was conscious, it could increase the anxiety, pain, and discomfort during the procedure.<sup>[14]</sup> Furthermore, the analgesic effect gradually begins after about 20 min and requires a large amount of medicine. Unpredictable complications such as epidural hematoma and meningitis spastic arachnoiditis may occur, or patients will not accept this method for fear of permanent damage to the nerves, although this possibility is rare in reality.<sup>[15]</sup> Evidence showed the combined EA-GA might attenuate intraoperative hemodynamic responses and improve postoperative cellular immunity so that it might be a more available anesthesia method for gallbladder cancer (GBC) patients.<sup>[16]</sup>

A part of the hemodynamic changes that occur during laparoscopic cholecystectomy (including decreased cardiac output, increased arterial pressure, increased systemic and pulmonary vascular resistance, and increased heart rate [HR]), in addition to the factors associated with the laparoscopic method (including the presence of air in the peritoneum, the patient's condition, and increased carbon dioxide) depends on the type of anesthesia.<sup>[17]</sup> Therefore, the selection of anesthetic technique with minimal effect on hemodynamics during laparoscopic cholecystectomy seems quintessential. Despite the prevalence of this type of surgery in Iran, there is still a dearth of widespread publication on the effects of EA on hemodynamic changes and its complications have not been addressed in this type of operation. Accordingly, this study will investigate and compare the effects of GA and EA on hemodynamic changes and their complications in patients undergoing laparoscopic cholecystectomy.

## Materials and Methods

This simple double-blind clinical trial study was performed on laparoscopic cholecystectomy patients undergoing EA or GA. Random sampling technique was performed among patients referring to operating room of Be'sat Hospital in Sanandaj, Iran, in 2015. The sample size was calculated based on that 20% difference in anesthetic doses is significant. Thirty-four patients per group were required to demonstrate a 20% difference in anesthetic doses at  $\alpha = 0.05$  and power of 90%. To exclude and dropouts, six more patients were added to each group. The patients were entered into the study using census technique and were randomly divided into two groups through double blocks method at the time of the study onset. The most important variable in this study

was blood pressure. Other hemodynamic variables were also associated in some way. To participate in the study, written consent form was taken from all the patients. The patient's candidate for laparoscopic cholecystectomy with American Society of Anesthesiologists Class I, Class II (Class I means a healthy person without any illness except the preceding case and Class II indicates a mild-to-moderate controlled systemic disease), and age range of 20–60 years old were included in the study. Exclusion criteria included severe cardiovascular diseases, neuropsychiatric disorders, severe metabolic diseases, drug abuse, any contraindications to neuraxial blockade as hypersensitivity to amide local anesthetics, bleeding or coagulation disorders, and infection at the injection site.

The group of EA received 18 ml of lidocaine 2%, plus epinephrine (1:200,000) plus 2 ml of sodium bicarbonate 8.4%. After negative aspiration, 3 ml of the solution was administered as a test dose. If after 2 min, there was no evidence of intravascular or subarachnoid injection, an additional 7 ml was injected over a 1.5 min period with fentanyl 50  $\mu\text{g}$ , and an additional 2 ml of the solution was administered incrementally to reach the desired level of segmental block. GA was induced with propofol (2–3 mg/kg), fentanyl citrate (5  $\mu\text{g}/\text{kg}$ ), and atracurium besylate (0.5 mg/kg). Balanced anesthesia was continued with sevoflurane, 1%–2% and propofol (2 mg/kg/h).

The required data were collected and recorded by a person other than the researcher to make the study double blinded. To measure variables, diastolic blood pressure (DBP), mean arterial pressure, systolic blood pressure (SBP), and pulse rate were measured at continuous intervals of immediately after induction; 5, 15, 30, and 45 min after anesthesia and during 1 h after anesthesia; at the end of surgery and 1, 2, 6, 12, and 24 h after surgery (and then determining the overall mean during the operation); and then in the recovery (twice for each patient) in both groups. Furthermore, the percentage of blood oxygen saturation was measured using a pulse oximetry device at intervals every half an hour during the operation (and then determining the percentage of oxygen saturation) and then in the recovery (once for each patient) in both groups. Preoperative arterial blood gases (ABGs) were compared with the postoperative ABGs in the recovery in both groups, and the postoperative pain was evaluated using visual analog scale in the recovery and the analgesic utilization during operation and recovery were examined in both groups.

The rate of postoperative nausea, itching, and shivering in the recovery was evaluated based on the patient's statements in both groups. Postoperative vomiting in recovery was recorded by observation in both groups. Duration of hospital stay, age, sex, and education was assessed based on patient records in both groups too.

Data were then entered into a questionnaire and analyzed using intention to treat protocol. The data of this study were entered into STATA-11 software (StataCorp. Timberlake (Ana Timberlake, UK). Quantitative descriptive objectives were calculated by calculating the mean and standard deviations, and if needed, other quantitative indicators such as mode and median were calculated. Qualitative descriptive objectives were also calculated by calculating ratios along with confidence intervals. For the analysis of qualitative objectives, Chi-square and Fisher's exact tests were run for single-variable analyses according to the data states. Furthermore, to compare the means of the two groups, *t*-test and in the absence of normal distribution, nonparametric tests were used to compare the means in the two groups. In the multivariate analysis, logistic regression was used for categorical variables.

### Results

In this study, among from 80 patients with laparoscopic cholecystectomy; 40 participants underwent GA including 26 (65%) females and 14 (35%) males with the mean age of  $50.10 \pm 9.78$  years old. Moreover, 40 participants underwent EA including 24 (60%) females and 16 (40%) males with the mean age of  $52.06 \pm 15.03$  years old ( $P > 0.05$ ) [Table 1].

As shown in Table 2, SBP values at times of t4, t5, t6, and t7 were considerably and significantly less than the time point of t0 in the GA group ( $P < 0.05$ ). In the EA group, SBP values at times t3, t4, t5, t6, and t7 were less than the time point of t0 ( $P < 0.05$ ). DBP and HR values at t3, t4, t5, t6, t7, t8, t9, and t10 times were significantly less than time point of t0 in each of the GA and EA groups ( $P < 0.05$ ). However, SpO<sub>2</sub> values in the GA group at time t3 and in the EA group at time t4 had a significant decrease compared to the time point of t0 ( $P < 0.05$ ).

In addition, the comparison of the mean values of these parameters at each follow-up time between the two groups showed that SBP values at times t1, t7, t8, t10, t11, and t12 were significantly higher in the EA group than in the GA group ( $P < 0.05$ ). Furthermore, DBP values at time t7, t9, and t10 in the EA group were greater than the GA

group ( $P < 0.05$ ). HR was significantly higher in the EA group at time t1 than in the GA group ( $P < 0.05$ ).

The severity of pain in patients immediately after surgery and at 1, 2, 6, 12, and 24 h after surgery in the GA group was significantly higher than the EA group ( $P < 0.05$ ) [Figure 1].

Finally, postoperative complications including shoulder pain, nausea, vomiting, itching, and hypertension were noted. There were only significant differences between the two side effects of shoulder pain and nausea in both groups, such that shoulder pain in GA group and nausea in the EA group were with 37.5% and 57.5% were the most frequent ones ( $P < 0.05$ ) [Table 2].

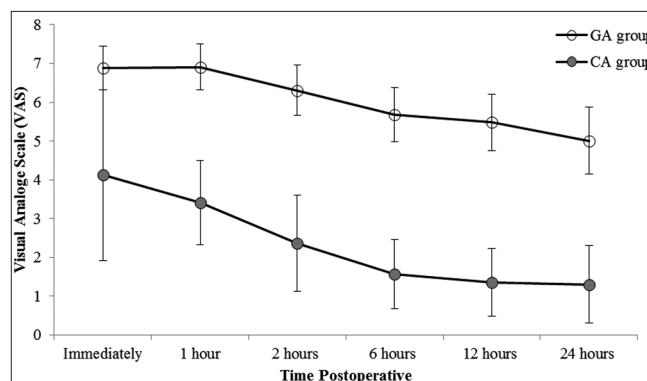
### Discussion

EA, today, has found great application in surgeries and control of its pain, obstetrics, and chronic pain. This type of anesthesia can be performed in a variety of ways, which are technically, physiologically, and pharmacologically different with each other. Our study showed that the mean duration of stay in the hospital was lower in the epidural group. The mean of SBP in the 1<sup>st</sup> h in the two groups was the highest, and in the next hour and 2 h after the anesthesia, the mean SBP decreased significantly, and from 4 h later, increased in both groups. In the GA group, the increase in SBP was much higher. Furthermore, the mean DBP in the 1<sup>st</sup> h had the highest value; however, it was higher in the GA group. The mean HR in the 1<sup>st</sup> h was in the highest level in both groups, but at 1 and 2 h after anesthesia, the mean HR dropped significantly. The mean oxygen saturation percentage in the 1<sup>st</sup> h in the two groups was the lowest, and in 1 and 2 h after anesthesia, the mean oxygen saturation increased somewhat, and after 4 h, the mean decreased in both groups; however, it was higher in the GA group. The mean arterial blood gas pressure in the 4 and 6 h after anesthesia in the two groups was at the lowest; however, it reached the highest level during the 2 h after anesthesia. Pain in the participants increased at 4, 6, and 12 h after anesthesia and it was more observed the GA group. The results of the study revealed that 1, 2, 4, 6,

**Table 1: Demographic characteristics of patients in the two groups**

Characteristics	GA group (n=40)	EA group (n=40)	P
Gender, n (%)			
Female	26 (65)	24 (60)	0.818
Male	14 (35)	16 (40)	
Age (years)	50.10±9.78	52.06±15.03	0.491
BMI (kg/m <sup>2</sup> )	27.23±4.42	27.10±3.64	0.886
Total surgery time (min)	53.71±7.83	57.42±10.25	0.072

Data showed mean±SD or n (%). BMI: Body mass index, SD: Standard deviation, EA: Epidural anesthesia, GA: General anesthesia



**Figure 1: Mean of postoperative pain evaluation**

**Table 2: Comparison of the mean clinical factors in two groups**

Time point	GA group (n=40)				EA group (n=40)			
	SBP (mmHg)	DBP (mmHg)	HR (beat/min)	SpO <sub>2</sub> (%)	SBP (mm Hg)	DBP (mmHg)	HR (beat/min)	SpO <sub>2</sub> (%)
t0	141.25±22.90	82.12±5.53	108.00±10.86	97.16±1.06	144.25±24.94	83.78±4.13	109.43±9.83	97.70±1.88
t1	133.70±13.46	81.55±4.08	104.86±11.53	97.15±1.10	138.50±4.82 <sup>†</sup>	82.46±5.33	107.00±13.78 <sup>†</sup>	97.34±0.27
t2	132.23±19.17	78.28±3.82*	98.29±24.73	97.00±0.99	135.25±15.19	77.14±4.58	105.29±11.30	97.56±1.20
t3	133.52±12.87	77.41±5.29*	95.28±19.73*	96.20±1.21*	133.00±20.41*	74.57±5.05* <sup>†</sup>	97.29±10.41*	97.04±1.06
t4	130.25±14.17*	73.14±5.92*	93.20±19.73*	96.83±0.84	131.24±14.69*	73.14±4.71*	96.00±11.23*	96.70±1.26*
t5	129.01±12.74*	73.14±5.08*	95.14±20.63*	97.00±1.34	131.01±12.32*	74.29±5.02*	95.32±11.30*	97.67±0.93
t6	127.52±10.46*	72.86±5.18*	97.85±22.56*	97.35±0.59	130.42±9.98*	74.00±4.97*	96.85±12.07*	97.70±1.25
t7	126.75±12.87*	71.34±12.61*	99.28±12.49*	97.20±0.96	132.16±12.87* <sup>†</sup>	75.99±5.44* <sup>†</sup>	97.28±11.84*	97.30±0.88
t8	133.44±14.05	73.66±12.45*	100.80±15.68*	97.55±0.78	138.65±8.43 <sup>†</sup>	76.14±4.07*	101.00±17.32*	97.71±1.06
t9	135.22±11.32	74.57±5.61*	103.42±23.31	98.05±1.17*	139.01±9.32	77.62±4.21* <sup>†</sup>	104.57±83.17	97.85±1.12
t10	135.64±16.27	75.10±7.07*	103.94±16.42	97.58±2.16	141.33±10.54 <sup>†</sup>	78.87±9.66* <sup>†</sup>	105.00±10.48	97.55±0.75
t11	137.11±17.53	79.76±5.93	104.01±9.87	97.87±2.52*	142.00±4.68 <sup>†</sup>	79.00±15.13	105.14±10.57	97.65±0.92
t12	138.10±9.87	80.11±5.93	106.43±13.65	97.92±2.44	143.16±6.62 <sup>†</sup>	82.14±4.70	107.42±22.07	97.67±0.76

\*Compared with t0 in the same group,  $P < 0.05$ , <sup>†</sup>Compared with the GA group at the same time point,  $P < 0.05$ . t0: Before anesthesia, t1: Immediately after anesthesia, t2: 5 min after anesthesia, t3: 15 min after anesthesia, t4: 30 min after anesthesia, t5: 45 min after anesthesia, t6: 1 h after anesthesia, t7: End of surgery, t8: 1 h after surgery, t9: 2 h after surgery, t10: 6 h after surgery, t11: 12 h after surgery, and t12: 24 h after surgery, GA: General anesthesia, EA: Epidural anesthesia, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, HR: Heart rate

and 12 h after anesthesia, there were statistically significant differences in two groups regarding pain severity. Results showed that vomiting was significantly less in the epidural group than in the general group. The results of our study indicated that there is no significant difference between the two groups regarding the severity of itching and shivering at different hours ( $P > 0.05$ ). In a study by Amit Gupta *et al.* (2011), the results showed that EA was effective for laparoscopic cholecystectomy for all patients, except for two people who needed to change the method to GA. The hemodynamic parameters and respiratory effects were maintained in the physiological range. Of these, only four people needed a vasopressor to treat hypotension and 15 had shoulder pain that was well controlled with a small dose of ketamine. Postoperative vomiting was seen in only three patients. The result was that thoracic EA with bupivacaine 0.75% and fentanyl for elective laparoscopic cholecystectomy is effective and maintains hemodynamic and ventilation changes during pneumoperitoneum with minimal complications requiring treatment in the physiological range.<sup>[18]</sup> In the study by Fujii *et al.*, at 24 h after surgery, pain score in Group A ( $2.3 \pm 1.2$ ) was lower than that in Group B ( $3.4 \pm 1.5$ ). However, 48 h later, no difference was observed between the two groups. As a result, the analysis of the comparison of EA and GA on hemodynamic changes and its complications in patients under laparoscopic cholecystectomy showed that EA with a combination of morphine and pbuti and vakaine relieves pain in patients 24 h after laparoscopic cholecystectomy.<sup>[9]</sup> In a study, the vital signs and the amount of oxygen saturation before, during, and after the operation; the variables of arterial blood gas analysis before and after the operation; pain; need for analgesia; complications; hospitalization; and mortality were recorded and compared. Vital signs and variables of analysis of

arterial blood gas did not differ significantly between the two groups. Although there was no significant difference between the two groups in pain severity, the dose of analgesia, and the duration of hospital stay, these variables were better in the thoracic EA group. No case of agitation, need for GA, complications, need for admission to intensive care unit, or mortality were observed. In the patients in need of diagnostic thoracoscopy, thoracic EA was at least equivalent to GA regarding signs and variables of arterial blood gas analysis. From pain and hospital stay after the operation, the thoracic EA was superior to GA, although this superiority was not statistically significant.<sup>[19]</sup> Khajavi *et al.*<sup>[20]</sup> conducted a research with regard to combined EA-GA versus GA in elective lumbar spine disk surgery, and they demonstrated that the combined anesthesia contributed to lower mean arterial blood pressure and HR, as well as reduced pain score in the combined EA-GA group during the postoperative period. Interestingly, Senoglu *et al.*<sup>[11]</sup> demonstrate that the patients exhibit remarkably lower HR and blood pressure levels with combined epidural analgesia and GA during laparoscopic cholecystectomy than those with the GA. As Pei *et al.*<sup>[21]</sup> have reported that combined EA-GA results in a better clinical outcome by reducing the dosage of anesthetic agents to promote the intact and sustained immunological function.

## Conclusion

The results of this study indicated that thoracic EA in patients with laparoscopic cholecystectomy had a significant effect on factors such as SBP, DBP, and arterial oxygen saturation and that there was a statistically significant difference between the two groups. Furthermore, local anesthetic complications were less than the

general one. Therefore, this method is recommended for cholecystectomy.

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### Conflicts of interest

There are no conflicts of interest.

### References

1. Joris J, Cigarini I, Legrand M, Jacquet N, De Groote D, Franchimont P, *et al.* Metabolic and respiratory changes after cholecystectomy performed via laparotomy or laparoscopy. *Br J Anaesth* 1992;69:341-5.
2. Odeberg-Werner S. Laparoscopic surgery – Effects on circulatory and respiratory physiology: An overview. *Eur J Surg Suppl.* 2000; 585:4-11.
3. Yegin A, Erdogan A, Kayacan N, Karsli B. Early postoperative pain management after thoracic surgery; pre- and postoperative versus postoperative epidural analgesia: A randomised study. *Eur J Cardiothorac Surg* 2003;24:420-4.
4. Lee JH, Huh J, Kim DK, Gil JR, Min SW, Han SS, *et al.* Laparoscopic cholecystectomy under epidural anesthesia: A clinical feasibility study. *Korean J Anesthesiol* 2010;59:383-8.
5. Wahba RW, Mamazza J. Ventilatory requirements during laparoscopic cholecystectomy. *Can J Anaesth* 1993;40:206-10.
6. Sebel PS, Bowdle TA, Ghoneim MM, Rampil IJ, Padilla RE, Gan TJ, *et al.* The incidence of awareness during anesthesia: A multicenter United States study. *Anesth Analg* 2004;99:833-9.
7. Jenkins K, Baker AB. Consent and anaesthetic risk. *Anaesthesia* 2003;58:962-84.
8. American Society of Anesthesiologists. Continuum of Depth of Sedation Definition of General Anesthesia and Levels of Sedation/Analgesia. Amended 21 October, 2009. American Society of Anesthesiologists; 27 October, 2004. Available from: <http://www.asahq.org/publicationsAndServices/standards/20.pdf>. [Last accessed on 2009 Dec 01].
9. Fujii Y, Toyooka H, Tanaka H. Efficacy of thoracic epidural analgesia following laparoscopic cholecystectomy. *Eur J Anaesthesiol* 1998;15:342-4.
10. Safaeian R, Movasaghi GH. Comparison between incidence of postoperative nausea and vomiting after total abdominal hysterectomy in general and epidural anesthesia. *Razi J Med Sci* 2001;8:308-11.
11. Senoglu N, Yuzbasioglu MF, Oksuz H, Yildiz H, Dogan Z, Bulbuloglu E, *et al.* Effects of epidural-and-general anesthesia combined versus general anesthesia alone on femoral venous flow during laparoscopic cholecystectomy. *J Laparoendosc Adv Surg Tech A* 2010;20:219-23.
12. Savas JF, Litwack R, Davis K, Miller TA. Regional anesthesia as an alternative to general anesthesia for abdominal surgery in patients with severe pulmonary impairment. *Am J Surg* 2004;188:603-5.
13. Cheng YC, Cheng XB, Li XJ, Wang FZ, Li ZK. Combined general and regional anesthesia and effects on immune function in patients with benign ovarian tumors treated by laparoscopic therapy. *Int J Clin Exp Med* 2013;6:716-9.
14. Huppelschoten AG, Bijleveld K, Braams L, Schoot BC, van Vliet HA. Laparoscopic sterilization under local anesthesia with conscious sedation versus general anesthesia: Systematic review of the literature. *J Minim Invasive Gynecol* 2018;25:393-401.
15. Atkinson TM, Giraud GD, Togioka BM, Jones DB, Cigarroa JE. Cardiovascular and ventilatory consequences of laparoscopic surgery. *Circulation* 2017;135:700-10.
16. Zhu J, Zhang XR, Yang H. Effects of combined epidural and general anesthesia on intraoperative hemodynamic responses, postoperative cellular immunity, and prognosis in patients with gallbladder cancer: A randomized controlled trial. *Medicine (Baltimore)* 2017;96:e6137.
17. Gupta A, Gupta K, Gupta PK, Agarwal N, Rastogi B. Efficacy of thoracic epidural anesthesia for laparoscopic cholecystectomy. *Anesth Essays Res* 2011;5:138-41.
18. Fuji T, Wang CJ, Fujita S, Kawai Y, Nakamura M, Kimura T, *et al.* Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: The STARS E-3 trial. *Thromb Res* 2014;134:1198-204.
19. Zeng X, Jiang J, Yang L, Ding W. Epidural dexmedetomidine reduces the requirement of propofol during total intravenous anaesthesia and improves analgesia after surgery in patients undergoing open thoracic surgery. *Sci Rep* 2017;7:3992.
20. Khajavi MR, Asadian MA, Imani F, Etezadi F, Moharari RS, Amirjamshidi A, *et al.* General anesthesia versus combined epidural/general anesthesia for elective lumbar spine disc surgery: A randomized clinical trial comparing the impact of the two methods upon the outcome variables. *Surg Neurol Int* 2013;4:105.
21. Pei L, Tan G, Wang L, Guo W, Xiao B, Gao X, *et al.* Comparison of combined general-epidural anesthesia with general anesthesia effects on survival and cancer recurrence: A meta-analysis of retrospective and prospective studies. *PLoS One* 2014;9:e114667.