International Journal of Pain & Relief

Research Article

Low *versus* High Concentration Bupivacaine in Thoracic Epidural for Perioperative Analgesia: A Retrospective Study

Vandana Sharma*, Ji Yoon Baek, Seokhyun Jin, Han Ying Zhang and George Padkowsky

Department of Anesthesiology, SUNY Upstate Medical University, Syracuse, New York, USA

***Address for Correspondence:** Vandana Sharma, Department of Anesthesiology, SUNY Upstate Medical University, Syracuse, New York, USA, Tel: +1-315-464-4259; ORCID: orcid.org/0000-0003-4581-1029; E-mail: sharmav@upstate.edu

Submitted: 15 September 2021; **Approved:** 02 October 2021; **Published:** 04 October 2021

Cite this article: Sharma V, Baek JY, Jin S, Zhang HY, Padkowsky G. Low *versus* High Concentration Bupivacaine in Thoracic Epidural for Perioperative Analgesia: A Retrospective Study. Int J Pain Relief. 2021 Oct 04; 5(1): 010-015.

ISSN: 2640-5539

ISSN: 2640-5539

ABSTRACT

Objectives: In order to analyze which thoracic epidural concentration would provide satisfactory pain relief while minimizing the incidence of hypotension, the efficacy of Low Concentration Bupivacaine 0.0625% (LCB) was compared with High Concentration Bupivacaine 0.125% (HCB).

Methods: Data was collected from the electronic medical record. Primary outcomes are pain control and the incidence of hypotension compared between the 2 different concentration groups. Secondary outcomes are incidence of complications (nausea/vomiting, positional headache, and sedation), time to ambulate, time to oral intake, and patient satisfaction scores.

Results: Out of 109 patients, 68 patients received LCB and 41 patients received HCB. No difference was observed in NRS pain score or functional pain scores. However, the incidence of inadequate pain control in the LCB group is significantly higher than the HCB group ($p < 0.05$). The incidence of hypotension was not significantly different. There was no significant difference in overall complication, nausea and vomiting, positional headache, and sedation. Subgroup analysis of 38 hepatobiliary surgical patients showed no difference in NRS pain score, functional pain scores, or incidence of hypotension. Though not statistically significant, there was a trend towards inadequate pain control in LCB group.

Discussion: There is superior pain control in the HCB group, and the difference in hypotension between the 2 groups is not as drastic as previously believed. Therefore, HCB may be used as the starting concentration, making changes as needed. Additionally, if the primary surgical team is on board, vasopressors may be used to temporarily manage postoperative hypotension.

Keywords: Thoracic; Epidural; Bupivacaine; Concentration; Hypotension

INTRODUCTION

Hypotension is a commonly seen phenomenon in the perioperative period due to effects of general anesthesia and intravascular fluid shifts associated with major abdominal surgery. Perioperative systemic hypotension can lead to end organ hypoperfusion, with effects that directly correlate with the severity of hypotension [1]. A systematic review demonstrated that optimization of blood pressure in perioperative period could reduce the incidence of postoperative acute kidney injury [2]. Similarly, there is strong association detected between severity of intraoperative hypotension and increased 30-day mortality after non-cardiac surgery [3].

Thoracic epidural analgesia is considered gold standard for perioperative pain control after major abdominal or thoracic surgery due to its favorable effects on pulmonary outcomes, gastric motility, early mobilization and reduced opioid consumption [4,5]. The postoperative beneficial effects of epidural analgesia were further reinforced in a systematic review by Rodgers, et al. [6] which demonstrated neuraxial analgesia resulted in reduced postoperative mortality and morbidity [7]. Thoracic epidural analgesia is commonly used as adjunct to general anesthesia during open hepatobiliary procedures. Safety of thoracic epidural analgesia has been debated in hepatobiliary surgery especially during hepatic resection due to unpredictable coagulation profile and periods of hemodynamic instability in the postoperative period, but no studies have demonstrated a higher incidence of epidural hematoma in patients undergoing these procedures. With the advent of field blocks and fast track surgeries, it is unfortunate that the gold-standard thoracic epidural analgesia is falling out of favor for managing postoperative pain after hepatobiliary procedures. Part of this problem can also be attributed to the lack of trained personnel to manage epidural infusions after hours and high failure rate of epidural analgesia.

One of the challenges associated with thoracic epidural local anesthetic infusion is accentuation of systemic hypotension due to blockade of spinal sympathetic nerve fibers in the thoracic region. In an effort to avoid the disastrous end organ effects of hypotension, interruptions in epidural infusion during surgery and immediately after are common, leading to unsatisfactory pain control at the cost of optimizing the hemodynamics.

At our institution, thoracic epidural analgesia is the most practiced method of pain management after open hepatobiliary surgery. Optimizing pain control in these patients while maintaining stable hemodynamics during the first 24-48 hours in the postoperative period requires a careful titration of epidural infusion by the acute pain service and can be a challenging task. In an endeavor to analyze which epidural concentration would provide satisfactory pain relief while minimizing the incidence of hypotension during open hepatobiliary cases, we performed this quality project comparing the efficacy of thoracic epidural infusion containing Low Concentration Bupivacaine (0.0625%) (LCB) with High Concentration Bupivacaine (0.125%) (HCB).

MATERIALS AND METHODS

This study was initiated as an institutional quality improvement project designed as a retrospective review and was therefore exempt from IRB approval. IRB identification number of this study is 1517345-3. The study included all patients between ages 18 and 65 years who underwent major abdominal surgeries (Appendix 1) between 12/16/2019 and 5/9/21, primarily utilizing lower thoracic epidural catheter infusion (T8-T11) for postoperative analgesia.

We excluded patients with pregnancy, extremes of age, pre-existing uncontrolled hypertension or severe hemodynamic instability peri-operatively. We also excluded patients with upper thoracic (any level above T5) or lumbar epidurals and those patients with inadequate data due to insufficient documentation on Electronic Medical Record (EMR) (Figure 1).

Data was collected from the EMR (Epic software from Epic Systems Corporation) by the research team, after the patients were transported to the wards or the ICU postoperatively.

At our institution, 2 different concentrations of bupivacaine are utilized for epidural analgesia infusion- Low Concentration Bupivacaine (LCB) of 0.0625% or High Concentration Bupivacaine (HCB) of 0.125%. Bupivacaine is usually combined with an opioid, either fentanyl (2 mcg/ml) or hydromorphone (10 mcg/ml). We wanted to know if one concentration of epidural infusion results in better pain control and higher patient satisfaction score, compared to the other concentration without leading to significant hemodynamic

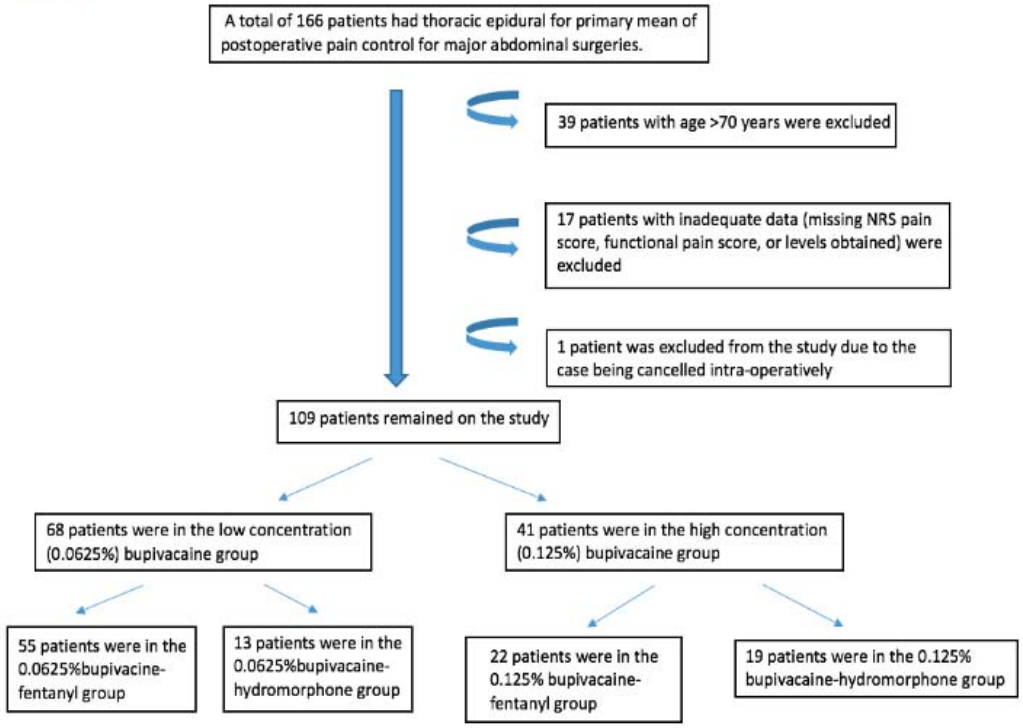

Figure 1: Patient inclusion. Flow diagram illustrating patient inclusion and reason for exclusion.

instability. We hypothesized that the pain control would be similar between the LCB and HCB groups but that HCB would result in higher incidence of hemodynamic instability.

The primary outcomes of this study were pain control and the incidence of hypotension compared between the two different concentration groups. Secondary outcomes included the incidence of complications associated with the thoracic epidural (nausea/vomiting, positional headache, and sedation), time to ambulate, time to oral intake, and patient satisfaction scores. In analyzing the outcomes, the patients were matched with respect to their age, gender and ASA status.

Out of 109 cases analyzed, 50 cases involved hepatobiliary surgeries including partial and total hepatectomies, liver resection, pancreatic biopsy, and Whipple procedure. Subgroup analysis was done on these cases, comparing the incidences of inadequate pain control and hypotension between the LCB and HCB groups.

Statistical analysis was performed by utilizing SAS version 9.4 and Pearson's chi squared test or 2 sample t-test was utilized, except when there were less than 5 individuals in a category being analyzed, Fisher's exact test was utilized. A p-value of <0.05 was considered to be statistically significant for each statistical test performed.

The effectiveness of pain control of LCB and HCB groups were assessed by comparing the NRS pain scores, functional pain scores, and satisfaction scores, using Pearson's chi squared tests (Appendix 2). The incidence of inadequate pain control and failed epidural (as defined in Appendix 3) were compared between the two groups utilizing two sample t-test.

The incidence of hypotension compared between the LCB and HCB groups was done by utilizing 2 sample t-test. Additionally, the incidence of other complications (nausea/vomiting, positional headache, and sedation), mean time to ambulate and the mean time to clears were compared between the two different bupivacaine concentration groups utilizing 2 sample t-test.

RESULTS

Out of 109 patients, 68 patients received LCB (low concentration bupivacaine 0.0625%) and 41 patients received HCB (high concentration bupivacaine 0.125%) who fulfilled inclusion and exclusion criteria. The baseline demographics of the two treatment groups are reported in table 1. The patients were similar in terms of age, gender and ASA level. We compared NRS pain score, functional pain score and satisfaction score between the two groups. No difference was observed in NRS pain score or functional pain score on POD1 and POD2 between the two groups. However, the incidence of inadequate pain control in the

Table 1: Demographics of patients who received LCB (Low Concentration Bupivacaine 0.0625%) and HCB (High Concentration Bupivacaine 0.125%) who underwent major abdominal surgeries.

	LCB (n = 68)	HCB (n = 41)	p value
Age			0.258
< = 65	50 (73.53)	34(82.93)	
> 65	18(26.47)	7(17.07)	
Gender			0.096
Female	27(39.71)	23(56.10)	
Male	41(60.29)	18(43.90)	
ASA			0.363
2	8(11.76)	8(20.00)	
3	53(77.94)	30(75.00)	
4	7(10.29)	2(5.00)	

ISSN: 2640-5539

Table 2: Comparison in pain score on Postoperative Day (POD) 1 and 2, functional pain score on POD 1 and 2, inadequate pain control, sensory level, patient satisfaction score, overall complication, hypotension, nausea/vomiting, positional headache, sedation, failed epidural, time to ambulate and time to clear liquid between the LCB group and the HCB group who underwent major abdominal surgeries.

	LCB (*n* = 68)	HCB (*n* = 41)	*p* value
Pain score POD 1			0.341
0	8(11.76)	7(17.07)	
1-4	42(61.76)	18(43.90)	
5-7	13(19.12)	11(26.83)	
8-10	5(7.35)	5(12.20)	
Pain score POD 2			0.350*
0	12(17.91)	9(21.95)	
1-4	41(61.19)	24(58.54)	
5-7	13(19.40)	5(12.20)	
8-10	1(1.49)	3(7.32)	
Functional pain score POD 1			0.930*
0	5(7.35)	4(9.76)	
1-2	56(82.35)	34(82.93)	
3	5(7.35)	2(4.88)	
4-5	2(2.94)	1(2.44)	
Functional pain score POD 2			1.000*
0	8(11.94)	4(9.76)	
1-2	56(83.58)	35(85.37)	
3	3(4.48)	2(4.88)	
4-5	0(0.00)	0(0.00)	
Inadequate pain control	21(30.88)	2(4.88)	**0.001**^
Patient satisfaction score			0.302*
0	2(3.57)	0(0.00)	
1	8(14.29)	2(5.56)	
2	46(82.14)	34(94.44)	
Overall complication	21(30.88)	15(36.59)	0.540
Hypotension	17(25.00)	12(29.27)	0.625
Nausea/Vomiting	5(7.35)	5(12.20)	0.498*
Positional headache	0(0.00)	1(2.44)	0.376*
Sedation	2(2.94)	0(0.00)	0.526*
Failed epidural	4(5.88)	5(12.50)	0.287*
Time to ambulate			0.766
Mean (SD)	1.4(0.84)	1.5(1.08)	
Time to clears			0.481
Mean (SD)	1.2(0.82)	1.3(0.80)	
			^ = *p* value < 0.05, * = Fisher's exact test

Table 3: Subgroup analysis.
Comparison in pain score on Postoperative Day (POD) 1 and 2, functional pain score on POD 1 and 2, inadequate pain control, sensory level, hypotension between the LCB group and the HCB group who underwent hepatobiliary surgeries.

	LCB (*n* = 38)	HCB (*n* = 12)	*p* value
Gender			0.411
Female	17(44.74)	7(58.33)	
Male	21(55.26)	5(41.67)	
Pain score POD1			0.106*
0	3(7.89)	2(16.67)	
1-4	26(68.42)	4(33.33)	
5-7	6(15.79)	5(41.67)	
8-10	3(7.89)	1(8.33)	
Pain score POD2			0.300*
0	4(10.81)	2(16.67)	
1-4	26(70.27)	8(66.67)	
5-7	7(18.92)	1(8.33)	
8-10	0(0.00)	1(8.33)	
Functional pain score POD1			0.539*
0	2(5.26)	1(8.33)	
1-2	32(84.21)	9(75.00)	
3	4(10.53)	2(16.67)	
Functional pain score POD2			0.522*
0	3(8.11)	0(0.00)	
1-2	33(89.19)	11(91.67)	
3	1(2.70)	1(8.33)	
4	0(0.00)	0(0.00)	
Inadequate pain control	13(34.21)	2(16.67)	0.304*
Hypotension	11(28.95)	3(25.00)	1.000*
			* = Fisher's exact test

LCB group is significantly higher than the HCB group. ($p < 0.05$) No significant difference was observed in satisfaction score between the two groups (Table 2).

We also compared the incidence of hypotension between the two groups and there was no significant difference observed. There was no significant difference in terms of overall complication, nausea and vomiting, positional headache, and sedation between the two groups. The difference in terms of time to ambulate and time to clears was not observed between the two groups (Table 2).

We defined failed epidural as mentioned in Appendix 3 and reported 4.5% of failed epidural rate in our institution which is comparable to 12%-23% from other institutions. There was no significant between-group difference according to incidence of failed epidural (Table 2).

We performed subgroup analysis to compare the outcomes of any hepatobiliary surgeries only and to minimize bias from the variation of procedures. We also identified a total of 38 patients undergoing hepatobiliary procedures managed with LCB with opiates and

12 patients managed with HCB with opiates, who underwent hepatobiliary surgery.

The comparison in terms of NRS pain score and functional pain score is displayed in table 3. There was no difference in NRS pain score or functional pain scores on POD1 and POD2 between the two groups. No difference was observed in functional pain score on POD1 and POD2 between the two groups. Even though we did not detect a statistically significant difference in terms of inadequate pain control, there was a trend toward inadequate pain control in the LCB group (34% of patients in LCB group was found to have inadequate pain control, compared to 17% of patient in HCB group). There was no significant difference in terms of incidence of hypotension the two groups which is similar to our result from the main study (Table 3).

Overall we found that there was no difference in terms of hemodynamic changes between the two groups (LCB *vs.* HCB) but there was a higher incidence of inadequate pain control among patients receiving LCB.

DISCUSSION

Thoracic Epidural Anesthesia (TEA) is often considered the gold standard for pain control after major abdominal or thoracic surgeries; however, overall utilization of TEA has decreased over the years with the advent of field blocks and fast track surgeries. The benefits of thoracic epidurals include reduced opioid consumption, early gastric motility, early mobilization, and decreased postoperative pulmonary complications [4,8]. However, they can be difficult to manage because they require balancing pain control with systemic hypotension, often encountered the first 24-48 hours after surgery due to intraoperative blood loss and fluid shifts. Other barriers to delivery of effective epidural analgesia include epidural failure, inadequate sensory blockade, and availability of staff required to manage catheters while in place.

The goal of this study was to determine which epidural infusion concentration is associated with best pain control while minimizing the hemodynamic changes. At our institution two different concentrations of local anesthetic are used for our epidural infusions, Low Concentration (LCB) defined as 0.0625% bupivacaine with opioid, and High Concentration (HCB) defined as 0.125% bupivacaine with opioid. We hypothesized that LCB would reduce the incidence of hypotension as a result of less sympathectomy while providing similar analgesic efficacy as HCB thus receiving all the benefits of analgesia while encountering fewer side effects.

Various local anesthetics and concentrations may be administered via epidural and the optimal concentration of bupivacaine to achieve effective analgesia while minimizing adverse effects has been a topic of heated discussion. Bupivacaine is a commonly used local anesthetic in epidural infusions. High Concentration Bupivacaine (HCB) is thought to produce faster onset and longer duration of block than Low Concentration Bupivacaine (LCB) thereby providing more effective analgesia [9,10]. However, hypotension is an unwanted side effect often seen in patients with thoracic epidural infusion caused by sympathetic nerve blockade by the local anesthetic leading to vasodilation and hypotension. These hemodynamic effects are exacerbated by hypovolemia [11]. In a study by Ginosar, et al. [12] the authors found HCB may lead to higher degree of sympathectomy-mediated vasodilation. For this reason, many anesthesiologists prefer to start with LCB particularly in patients that are considered high risk for hypotension, for example elderly patients, patients with pre-existing cardiac disease, or those undergoing procedures associated with large intravascular volume shifts or large blood volume loss. Contrary to our hypothesis we found there was no difference in the incidence of hypotension between the two groups whereas the LCB group showed higher incidence of inadequate pain control. The incidence of inadequate pain control that necessitated a change in epidural infusion rate or concentration was significantly higher in the LCB group ($p = 0.001$). Our overall percentage of failed epidurals was 8.3%. Based on available data the overall failure rate of thoracic epidurals has been reported as high as 30% at some institutions with the low end reported around 5% [13].

Thoracic epidurals can provide excellent analgesia, spanning many abdominal dermatomes for a large variety of procedures. It is particularly useful for large laparotomies, chevron incisions, or midline incisions with flank extensions (L-shaped). Appropriate placement of a mid-thoracic epidural will provide analgesia for several thoracic segments above and below the level placed but also has several physiologic implications, both positive and negative. One of the most commonly encountered side effects is hypotension caused by differentiation of cardiac and thoracic sympathetic outflow. Systemic vasomotor tone is primarily controlled by sympathetic fibers arising from T5-L1 nerve roots. Dampening of these signals leads to arterial and venous dilatation along with decreased endogenous catecholamine release also controlled by the sympathetic nervous system. Cardiac accelerator fibers found from T1-T4 may be affected with high blockade, preventing an appropriate increase in heart rate with decreased contractility ultimately leading to worsening hypotension [14]. The effects of deafferentation of cardiac sympathetic outflow is still currently being studied but has been clearly implicated in decreased heart rate, central venous pressure, and cardiac output [15] as well as increased coronary blood flow due to dampened coronary vasoconstriction controlled by sympathetic signals [16]. These effects may be protective in ways but also have unwanted consequences as perfusion is decreased with instances of hypotension at surgical sites. Other organ systems are also affected by thoracic epidural infusions including pulmonary, genitourinary and gastrointestinal. Abdominal and intercostal muscle contribution to inspiration is somewhat reduced given the distribution of blockade from the epidural, though the diaphragm is spared due to its innervation arising from the cervical spine. As a result, FEV1 and VC are mildly reduced in patients with thoracic epidural. However, patients without thoracic epidural, in significant post operative pain and unable to take adequately deep breaths, have been shown to have significantly more reduction in FEV and VC, and typically have more incidence of atelectasis [17] than those with thoracic epidural in place.

This study included procedures from all surgical disciplines. A large subset of the data collected included hepatobiliary cases. A subgroup analysis was performed for the hepatobiliary surgeries for all parameters listed previously in order to create a homogenous data set for further evaluation. There was not a significant difference in inadequate pain control, functional pain score, or hypotension between LCB and HCB in the hepatobiliary group. Although there was no statistically significant difference between the groups, there was a much greater incidence of reporting inadequate pain control in the LCB group.

This was a retrospective observational study which had some limitations. The regional anesthesiologist on service chose the

composition of the epidural infusion for the epidurals placed and supervised that day. As a consequence of this, the sicker patients, particularly those undergoing extensive hepatobiliary surgery would be started on LCB first and then switched to higher concentration if pain was uncontrolled and hemodynamic stability was present. This resulted in significantly more patients with LCB solution (n = 68) compared to those with HCB solution (n = 41). The study had large variability in types of surgery from all disciplines, and for this reason a subgroup was analyzed for more uniformity. The method to establish baseline blood pressure was not standardized. For patients who were seen at the Preadmission Testing clinic (PAT), the baseline blood pressure was established at that time. However, for patients who were not seen at PAT clinic, baseline blood pressure was determined on the day of surgery which may have been an overestimation due to preoperative anxiety. Although patients with significant hemodynamic instability were not included in the study, our study did not factor the Estimated Blood Loss (EBL) during surgery. Significant EBL is an independent risk factor for postoperative hypotension. Without consideration of EBL, it is difficult to determine whether postoperative hypotension was solely due to bupivacaine concentration or confounded by blood loss. This may have affected the analysis of data points, such as time to ambulate or time to clears that were collected later in the post-operative period.

There are no concrete guidelines in place for management of epidural infusion concentration or rates. It is up to the discretion of the physician on service to determine what concentration is most appropriate for each patient. A decision should be made that considers patient frailty and how extensive the procedure will be in order to maximize analgesia while minimizing chances of hypotension. From our study, we have noted that there is superior pain control in the HCB group, and that the difference in hypotension between the two groups is not as drastic as previously believed. With this data in mind, we could attempt using HCB as the starting concentration and making changes as needed on a case-by-case basis. Additionally, use of vasopressors to temporarily manage post-surgical hypotension can be utilized if the primary surgical team is on board. Randomized controlled trials are necessary to further investigate the relationship between the bupivacaine concentration and the hemodynamic response.

REFERENCES

1. Gregory A, Stapelfeldt WH, Khanna AK, Smischney NJ, Boero IJ, Chen Q, Stevens M, Shaw AD. Intraoperative Hypotension Is Associated With Adverse Clinical Outcomes After Noncardiac Surgery. Anesth Analg. 2021 Jun 1;132(6):1654-1665. doi: 10.1213/ANE.0000000000005250. PMID: 33177322; PMCID: PMC8115733.
2. Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med. 2009 Jun;37(6):2079-90. doi: 10.1097/CCM.0b013e3181a00a43. PMID: 19384211.
3. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology. 2015 Aug;123(2):307-19. doi: 10.1097/ALN.0000000000000756. Erratum in: Anesthesiology. 2016 Mar;124(3):741-2. PMID: 26083768.
4. Pöpping DM, Elia N, Marret E, Remy C, Tramèr MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg. 2008 Oct;143(10):990-9; discussion 1000. doi: 10.1001/archsurg.143.10.990. PMID: 18936379.
5. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, Collins KS; MASTER Anaethesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002 Apr 13;359(9314):1276-82. doi: 10.1016/S0140-6736(02)08266-1. PMID: 11965272.
6. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000 Dec 16;321(7275):1493. doi: 10.1136/bmj.321.7275.1493. PMID: 11118174; PMCID: PMC27550.
7. Guay J, Choi PT, Suresh S, Albert N, Kopp S, Pace NL. Neuraxial anesthesia for the prevention of postoperative mortality and major morbidity: an overview of cochrane systematic reviews. Anesth Analg. 2014 Sep;119(3):716-725. doi: 10.1213/ANE.0000000000000339. PMID: 24977635.
8. Zingg U, Miskovic D, Hamel CT, Erni L, Oertli D, Metzger U. Influence of thoracic epidural analgesia on postoperative pain relief and ileus after laparoscopic colorectal resection : Benefit with epidural analgesia. Surg Endosc. 2009 Feb;23(2):276-82. doi: 10.1007/s00464-008-9888-x. Epub 2008 Mar 25. PMID: 18363059.
9. Duggan J, Bowler GM, McClure JH, Wildsmith JA. Extradural block with bupivacaine: influence of dose, volume, concentration and patient characteristics. Br J Anaesth. 1988 Sep;61(3):324-31. doi: 10.1093/bja/61.3.324. PMID: 3179151.
10. Murdoch JA, Dickson UK, Wilson PA, Berman JS, Gad-Elrab RR, Scott NB. The efficacy and safety of three concentrations of levobupivacaine administered as a continuous epidural infusion in patients undergoing orthopedic surgery. Anesth Analg. 2002 Feb;94(2):438-44, table of contents. doi: 10.1097/00000539-200202000-00040. PMID: 11812715.
11. Mendola C, Ferrante D, Oldani E, Cammarota G, Cecci G, Vaschetto R, Della Corte F. Thoracic epidural analgesia in post-thoracotomy patients: comparison of three different concentrations of levobupivacaine and sufentanil. Br J Anaesth. 2009 Mar;102(3):418-23. doi: 10.1093/bja/aep004. Epub 2009 Feb 3. PMID: 19189982.
12. Ginosar Y, Weiniger CF, Kurz V, Babchenko A, Nitzan M, Davidson E. Sympathectomy-mediated vasodilatation: a randomized concentration ranging study of epidural bupivacaine. Can J Anaesth. 2009 Mar;56(3):213-21. doi: 10.1007/s12630-008-9036-z. Epub 2009 Jan 28. Erratum in: Can J Anaesth. 2010 Jun;57(6):626. PMID: 19247742.
13. Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: causes and management. Br J Anaesth. 2012 Aug;109(2):144-54. doi: 10.1093/bja/aes214. Epub 2012 Jun 26. PMID: 22735301.
14. Veering BT, Cousins MJ. Cardiovascular and pulmonary effects of epidural anaesthesia. Anaesth Intensive Care. 2000 Dec;28(6):620-35. doi: 10.1177/0310057X0002800603. PMID: 11153287.
15. Clemente A, Carli F. The physiological effects of thoracic epidural anesthesia and analgesia on the cardiovascular, respiratory and gastrointestinal systems. Minerva Anestesiol. 2008 Oct;74(10):549-63. PMID: 18854796.
16. Buffington CW, Feigl EO. Adrenergic coronary vasoconstriction in the presence of coronary stenosis in the dog. Circ Res. 1981 Mar;48(3):416-23. doi: 10.1161/01.res.48.3.416. PMID: 7460214.
17. Tenenbein PK, Debrouwere R, Maguire D, Duke PC, Muirhead B, Enns J, Meyers M, Wolfe K, Kowalski SE. Thoracic epidural analgesia improves pulmonary function in patients undergoing cardiac surgery. Can J Anaesth. 2008 Jun;55(6):344-50. doi: 10.1007/BF03021489. PMID: 18566197.
18. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain. 2011 Oct;152(10):2399-2404. doi: 10.1016/j.pain.2011.07.005. PMID: 21856077.