Original Article

The Comparative Study of Epidural Levobupivacaine and Bupivacaine in Major Abdominal Surgeries in Type-2 Diabetic Patient

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Abstract

Background: *Major abdominal surgeries still induce neurohumoral changes responsible for postoperative pain, various organ dysfunctions, prolong hospitalization and convalescence. Insufficient pain therapy prolongs the hospital stay and rises the mortality rates. Epidural analgesia confers excellent pain relief and complete dynamic analgesia leading to a substantial reduction in the surgical stress response. Opioid and local anaesthetic infusion by an epidural catheter is widely used as a postoperative pain management method after major abdominal surgeries. Type-2 Diabetic patient has many comorbidity with cardiovascular complication and they are more vulnerable to pain.*

Objectives: *The purpose of this study was to compare the effect of levobupivacaine and bupivacaine with fentanyl in postoperative analgesia and haemodynamic changes of type-2 Diabetic patients for major abdominal surgeries.*

Material and method: *Sixty (60) patients were selected whose were suffering from Type-2 Diabetes mellitus and were going to be operated for major abdominal surgeries (Whipple's procedure, FCPD, Gastrectomy, Hemi colectomy). Every patient received an epidural block in the sitting position at the T_{8-9} or T_{9-10} level via 18 G Touhy needle. Each patient in group A received 0.125% levobupivacaine with 2 µgm. fentanyl / ml solution through epidural catheter @ 4 ml / hr. and group B were received 0.125% bupivacaine with 2 µgm. fentanyl / ml solution through epidural catheter@ 4 ml / hr*

Results: *Mean visual analog scale (VAS) values of groups did not differ at all time. They were 6 at the end of the surgery (0.Min, p= 0.06). The VAS scores were not statistically significant in group A & group B (p > 0.05). The frequency of tachycardia was higher in group B that was bupivacaine group.*

Conclusion*: The results of our study suggest same concentration of epidural levobupivacaine and bupivacaine with fentanyl provide stable postoperative analgesia and both were found safe for the patients undergoing major abdominal surgery, but levobupivacaine is less tachycardic and safer for Type-2 Diabetic patient.*

Keywords: *Major abdominal surgery, thoracic epidural, levobupivacaine, type 2 DM.*

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Introduction

As is known, insufficient pain therapy prolongs the hospital stay and raises the mortality rates.[1] Epidural is commonly used for acute and chronic pain therapy by the placement of a catheter in epidural space. Consequently, lower doses of drugs can be used and the side effects reduce. More effective analgesia and early mobilization are the advantages.[2]

The postoperative pain scores can be made lower by using multimodal analgesia and continuous epidural analgesia.[3] Opioid and local anaesthetic infusion by an epidural catheter is widely used as a postoperative pain management method after

major abdominal surgeries.[4] There are several methods now a days to provide sufficient analgesia. The agents which cause less side effects but better quality of analgesia are more valuable.

Systemic toxicity results from excessive blood levels of local anaesthetics in central nervous system and cardiovascular system when they are injected intravenous (IV) by mistake.[5] They cause directly negative inotrophy, myocardial conduction abnormalities and arrhythmias. Arrhythmogenic effects of these drugs are related with repolarization of potassium, sodium and calcium channels.[6] Consequently with this mechanism, cardiac impulse conduction slows down, QRS complex widens, PR distance gets longer, atrioventricular block occurs and fatal ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation occurs.[7]

As we know that Type-2 Diabetic patient has many co-morbidity with cardiovascular and renal complication, levobupivacaine shows less cardio toxic effect than bupivacaine, so for better postoperative pain management of diabetic patient with less complication.

Diabetes mellitus is the most common endocrine abnormality encountered in surgical patients and is associated with increased perioperative morbidity and mortality mainly due to the complications of the disease. Diabetes mellitus is characterized by impairment of carbohydrate metabolism caused by a deficiency of insulin activity which leads to hyperglycemia and glycosuria.[8] Surgery especially in the presence of general anaesthesia produces a diabetogenic response. Surgical stress leads to reproducible physiological, metabolic and hormonal responses, characterized by on altered carbohydrate metabolism, a net loss of protein and an increased lipolysis. They are due to an increased secretion of catecholamines, ACTH, cortisol and cytokines.[9] Cortisol prolongs and amplifies the hyperglycaemic effects of catecholamines by stimulating gluconeogenesis, and by increasing insulin resistance.[10] The increase in blood glucose in diabetic patients during the first hours of a stressful event is closely related to an increase in catecholamines.

The type of surgery plays an important role in severity of postoperative pain. Age, sex, psychological factors or pharmacological factors also plays an important role for postoperative pain.[11] The pain therapy after abdominal and thoracic surgeries is adequately successful by using continuous epidural infusion.[12]

Bupivacaine is a long-acting amide and widely used as local anaesthetic for epidural anaesthesia and analgesia. However bupivacaine induced cardiotoxicity in patients following accidental intravascular injection limits its use.[13] It has also potential for neurotoxicity.[14] Bupivacaine is found more toxic to both the central nervous system and the cardiovascular system.[15]

Therefore; a local anaesthetic which has similar effects a bupivacaine but has less side effects on cardiovascular system is needed. Levobupivacaine (S-1-butyl-2-piperidylformo-2, 6-xylididehydrochloride) is the pure S (-) - enantiomer of racemic bupivacaine. Preclinical animal and volunteer studies showed less cardiac toxicity than bupivacaine. It seems to be an alternative local anaesthetic agent in epidural anaesthesia and analgesia.

Our goal in this prospective, single blind, randomized study was to compare the levobupivacaine-fentanyl solution with bupivacaine-fentanyl solution in Type-2 Diabetic patients to determine the analgesic, hemodynamic and arrhythmogenic activity by recording VAS Score, NIBP and continuous ECG monitoring.

Material & methods:

This randomized single-blind study was conducted from 1st July '2014 to 31st December '2014 at the department of Anaesthesiology and Surgical ICU, BIRDEM General Hospital, Shahbagh, Dhaka, Bangladesh. After institutional ethical committee approval and informed written consent, a total number of 60 adult patients with Type - 2 Diabetes mellitus with ASA physical status II & III scheduled for various elective major abdominal surgeries under combined anaesthesia (General plus Epidural) were enrolled in this study. They were divided into two groups 30 in each group randomly allocated by envelop method where Group A (n=30) received 0.125% levobupivacaine with 2 μgm. fentanyl / ml solution through epidural catheter @ 4 ml / hr & Group B (n=30) receive 0.125% bupivacaine with 2 μgm. fentanyl / ml solution

through epidural catheter@ 4 ml / hr. All patients were reassured and the anaesthetic procedure was explained on the day before the operation. Intravenous access established in all patients in the operating room with base line arterial blood pressure (non-invasively) and heart rate obtained. Every patient was received an epidural block in the sitting position at the T8-9 or T9-10 level via 18 G Touhy needle. After epidural insertion each patient received 6-8 ml 0.125% levobupivacaine for group A and 0.125% bupivacaine for group B. Each patient received General anaesthesia with induction dose of inj. Fentanyl 2 microgram/kg, inj. Propofol 2mg/kg and muscle relaxant inj.Atracurium 0.5mg/kg. After induction, general anaesthesia was maintained by 60% N_2O and 40% O_2 and continuous infusion of Propofol @ 4mg/kg/hr - 6mg/kg/hr. An incremental dose of muscle relaxant inj. Atracurium $1/4^{th}$ of initial dose was given every 20 minutes interval.

Each patient in group A received 0.125% levobupivacaine with 2 µgm. fentanyl / ml solution through epidural catheter @ 4 ml / hr. and group B received 0.125% bupivacaine with 2 µgm. fentanyl / ml solution through epidural catheter@ 4 ml / hr just 15 minute after general anaesthesia.

The base line blood pressure and heart rate were recorded from the same

noninvasive monitor and cardiac rate and rhythm were also monitored from a continuous display of E.C.G from lead II. Blood sugar of each patient was monitored hourly in perioperative period.

Data processing:

All data presented as mean (standard deviation) unless otherwise indicated. Analysis of variance unpaired student t test and chi-square test used to detect the demographic data among the two groups. Chi-square test, with any correction needed (e.g., Yates's continuity correction) used to analyze the collected data. Data collected on a predesigned data collection sheet and later on compiled on a master chart. A p value of <0.05 accepted as statistically significant. Statistical analysis carried out using Statistical Package for Social Science (SPSS) for Windows version 17.0.

Result

Sixty patients who underwent major abdominal surgery were enrolled in the study. Among them 41 male and 19 female. Demographic data for each group was similar (Table1). No significant difference was obtained in systolic or diastolic pressure values between groups (Figure 1). Twelve patients (20%) underwent Whipples procedure, fifteen patients (25%) underwent triple bypass, twelve(20%) patients underwent biliary reconstruction, nine patients (15%) underwent anterior resection, six patients (10%) underwent total gastrectomy and six patients(10%) underwent partial gastrectomy

(Table 2). Mean duration of surgery for Whipple's procedure 4 hours, for Triple bypass 3.5 hours for Biliary reconstruction 3 hours, for Anterior resection 3 hours, for Total gastrectomy 2.5 hours and for Partial gastrectomy 2 hours (Table 2). Postoperative satisfaction with the epidural analgesia was similar with median scores of 69(levobupivacaine) and 73(bupivacaine) (VAS; 100mm= extremely satisfied) in the first 24 hour after operation.

There was no significant difference between groups for heart rate (Figure 1), systolic blood pressure (Figure 2), diastolic blood pressure (Figure 3) and postoperative analgesic requirements (Figure 4). Total drug consumption for group A was 720ml and for group B was 740 ml. Additional drug was needed for group A 56 ml and for group B 54ml . Sinus tachycardia was significantly higher in group B during postoperative period. The heart rate of patients in group B increased during postoperative first four hours but this result was not statistically significant.

Fourty patients Epidural catheter were inserted at the level of T8/9 out of which twenty two patients were group A and eighteen patients were group B. In twenty patients Epidural catheter were inserted at the level of T9/10 out of which eight patients were in group A and twelve patients were in group B.

ASA catagorization (II, III) of group A was 20/08 and of group B was 22/10 patients. No cases of cardiac depression or central nervous system toxicity caused by vascular absorption or direct intravascular injection of local anaesthetic occurred. Our postoperative repeated visits for early detection of pain and provide increased patient satisfaction.

Table 1 *Demographic variables*

Variables	Group-A	Group-B	p value
Age (years)	48.40±11.12	50.20±12.55	0.56^{ns}
Sex (M/F)	21/9	20/10	0.78^{ns}
Weight (kg)	66.30±9.44	67.67±8.13	0.55^{ns}

All values were presented as mean± SD or in frequencies. Data were analysed using unpaired student t-test. Statistically significance was set at p-value <0.05. (S=significance, NS=not significant)

Table-II *Distribution of the patients by type and duration of operation (n=60)*

Types of operation	Frequency	Percentage (%)	Duration of operation (hours) Mean±SD
Whilples	12	20.0	4.0±1.12
Triple bypass	15	25.0	3.5±0.85
Biliary reconstruction	12	20.0	3.12±0.75
Anterior resection	9	15.0	3.0±.65
Total gastrectomy	6	10.0	2.5±.63
Partial gastrectomy	6	10.0	2.0±.23
Total	60	100.0	3.33±0.60

All values were presented as mean± SD or in frequencies. Data were analysed using unpaired student t-test. Statistically significance was set at p-value <0.05. (S=significance, NS=not significant)

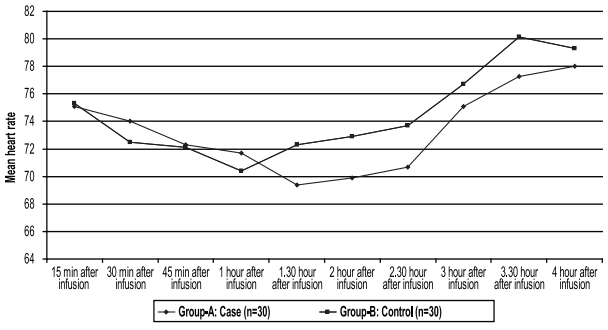

Fig 1 *Bar diagram showing per-operative heart rate in two groups*

The mean heart rate at different time in peroperative period compared between two groups. No statistical significant were observed in between groups (p > 0.05)

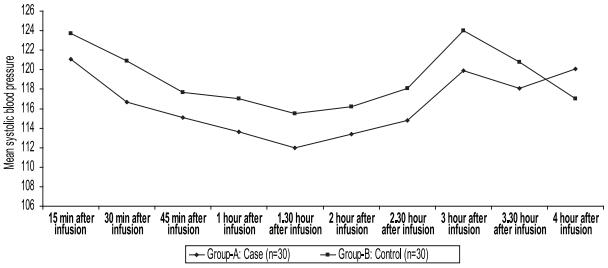

Fig 2 *Line diagram showing peroperative systolic blood pressure in two groups*

The mean systolic blood pressure at different time in peroperative period compared between two groups. No statistical significant were observed in between groups (p > 0.05)

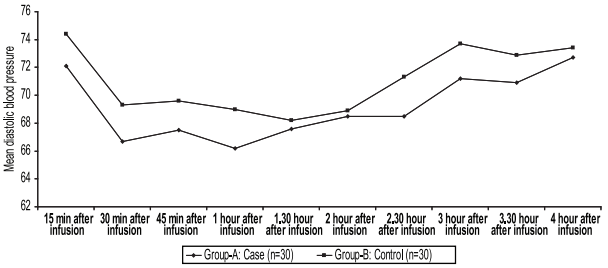

Fig 3 *Line diagram showing peroperative diastolic blood pressure in two groups*

The mean diastolic blood pressure at different time in peroperative period compared between two groups. No statistical significant were observed in between groups (p > 0.05)

Table-III

Comparison of heart rate at postoperative monitoring of the study respondents (n=60)

Heart rate	Group-A Mean±SD	Group-B Mean±SD	p value
0 hr immediate postoperative	78.3±3.9	81.6±3.0	<0.001s
1st hour after infusion	70.6±3.8	75.1±7.1	0.003s
3rd hour after infusion	68.5±6.7	75.8±5.7	<0.001s
5th hour after infusion	69.5±3.8	71.5±5.9	0.13 ns
7th hour after infusion	68.6±4.0	69.5±6.2	0.49 ns
9th hour after infusion	69.1±4.3	71.3±5.5	0.10 ns
11th hour after infusion	70.7±4.8	73.0±5.2	0.08ns
13th hour after infusion	68.9±5.2	71.6±7.1	0.09ns
15th hour after infusion	67.5±4.5	69.7±5.9	0.12ns
19th hour after infusion	67.9±3.6	68.2±6.5	0.84ns
24th hour after infusion	67.7±3.7	68.3±5.7	0.63ns

All values were presented as mean± SD or in frequencies. Data were analysed using unpaired student t-test. Statistically significance was set at p-value <0.05. (S=significance, NS=not significant)

The mean heart rate at immediate postoperative, 1st & 3rd hours were significantly higher in group B where as other period were non significant in between groups (p > 0.05).

Table-IV *Comparison of systolic blood pressure at postoperative monitoring of the study respondents (n=60)*

Systolic blood pressure	Group-A Mean±SD	Group-B Mean±SD	p value
0 hr immediate postoperative	124.4.9±7.0	127.3±5.7	0.09ns
1st hour after infusion	119.7±5.7	121.5±4.7	0.21ns
3rd hour after infusion	117.7±7.4	119.8±3.7	0.16ns
5th hour after infusion	114.9±7.1	118.1±4.1	0.08 ns
7th hour after infusion	112.6±9.3	115.5±3.9	0.12 ns
9th hour after infusion	112.9±8.1	115.5±4.1	0.13 ns
11th hour after infusion	113.2±8.5	114.1±6.5	0.63 ns
13th hour after infusion	113.7±8.9	115.5±4.4	0.34 ns
15th hour after infusion	112.7±8.2	115.8±4.2	0.07 ns
19th hour after infusion	110.7±7.8	113.5±4.9	0.10 ns
24th hour after infusion	114.1±9.2	112.5±5.2	0.41ns

All values were presented as mean± SD or in frequencies. Data were analysed using unpaired student t-test. Statistically significance was set at p-value <0.05. (S=significance, NS=not significant)

The mean systolic blood pressure at different time in postoperative period compared between two groups. No statistical significant were observed in between groups (p > 0.05)

Table-V *Comparison of diastolic blood pressure at postoperative monitoring of the study respondents (n=60)*

Diastolic blood pressure	Group-A (n=30) Mean±SD	Group-B (n=30) Mean±SD	p value
0 hr immediate postoperative	77.2±6.4	79.4±3.3	0.09ns
1st hour after infusion	68.2±6.4	71.0±6.4	0.09ns
3rd hour after infusion	67.7±7.7	69.6±4.0	0.23 ns
5th hour after infusion	69.7±6.5	68.9±4.2	0.52 ns
7th hour after infusion	68.0±4.8	69.4±3.0	0.18 ns
9th hour after infusion	69.0±6.6	69.7±4.9	0.65ns
11th hour after infusion	68.3±7.5	69.4±4.3	0.50ns
13th hour after infusion	66.8±7.9	69.2±5.2	0.18ns
15th hour after infusion	68.7±5.0	69.6±4.3	0.55ns
19th hour after infusion	67.6±5.0	67.9±5.7	0.81 ns
24th hour after infusion	65.7±5.0	67.5±3.9	0.12 ns

All values were presented as mean± SD or in frequencies. Data were analysed using unpaired student t-test. Statistically significance was set at p-value <0.05. (S=significance, NS=not significant).

The mean diastolic blood pressure at different time in postoperative period compared between two groups. No statistical significant were observed in between groups (p > 0.05).

The mean VAS at postoperative period compared between two groups. No statistical significant were observed in between groups (p > 0.05).

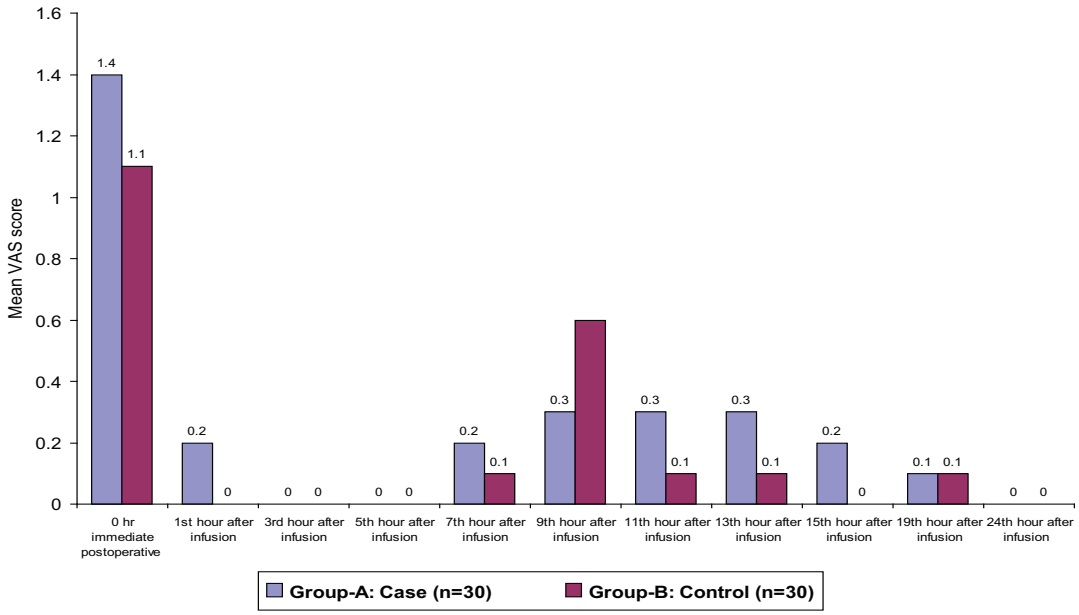

Fig 4 *Bar diagram showing postoperative VAS score in two groups*

Discussion

Epidural analgesia is considered as the gold standard analgesic technique for major abdominal surgeries. This strategy has the potential to provide complete analgesia and it is particularly effective at optimizing functional pain relief, thus improving patient satisfaction and postoperative outcome.

The postoperative stress response to major abdominal surgery is defined as a cascade of effects that result from activation of neural, metabolic and endocrine pathways with initiation of coagulation and inflammatory mechanisms.[20]

This postoperative surgical stress response could contribute to various organ dysfunctions in susceptible individuals, thus leading to a difficult and prolonged recovery and rehabilitation.[44] There is a common consensus that a reduction in the stress response is followed by a reduced postoperative major morbidity and improved surgical outcome.[20,44,45]

It has been postulated that pain relief represents an effective method to reduce surgical stress response, since afferent neural stimuli and activation of autonomic nervous system together with other reflexes by pain serve as a major release mechanism of the endocrine and metabolic responses.[44] Thus, one of the beneficial effects of epidural analgesia results from obtunding the postoperative stress response by provision of optimal analgesia. Many reported randomized studies with different analgesia regimens have been combined in meta-analysis, furthermore often there is no distinction between thoracic and lumber epidural blockade or various techniques of administration, facts that limit the interpretation of these findings.[44,46,47]

The use of well-documented physiological advantages of epidural analgesia in such a postoperative care program leads to decrease of morbidity across major abdominal procedures and significantly improves the quality of postoperative recovery.[48, 49]

Findings of many clinical trials are relevant in this respect. Thus, patients with major abdominal procedures managed in a multimodal care program including epidural analgesia have demonstrated earlier discharge from intensive –care unit, earlier return of normal bowel function, reduced catabolism and less fatigue than those undergoing equivalent surgery but not participating in such a postoperative care program.[20,48,50]

The present study demonstrates that levobupivacaine, the pure S (-) -enantiomer of racemic bupivacaine, is as effective as bupivacaine in epidural analgesia when used with fentanyl for major abdominal surgeries. Bupivacaine has been compare to levobupivacaine for epidural, spinal or infiltration anaesthesia and for supraclavicular brachial plexus block. The comparisons of these two local anaesthetics were planned for lower abdominal surgeries, lower limb surgeries or gynecologic surgeries.[23, 27] No significant difference for the quality of analgesia was recorded between these local agents and all of them provided efficient clinical anaesthesia.[28, 29]

In separate study we found that same concentration of epidural bupivacaine and levobupivacaine with fentanyl increased the incidence of supraventricular arrhythmias but the increase in bupivacaine group was significantly higher than levobupivacaine group. There was not significant variability in the frequencies of Ventricular arrhythmia levels both in preoperative and postoperative periods. The basic cardiac rhythm status of the patients was determined first by Holter machine before the operation. Then we compared the arrhythmogenic, analgesic and haemodynamic effects of bupivacaine and levobupivacaine in the postoperative period.

Bupivacaine produces local anaesthesia by blocking sodium channels and this action is main responsible for its Cardiotoxicity.[28] Levo-bupivacaine has less potential for sodium channel blocked and produces less arrhythmia, so it has been a popular local anaesthetic agent.[30,31] It was thought that it can be used instead of bupivacaine because of its less toxic side effects to cardiovascular and central nervous system.[32,33] Corrected QT is used to evaluate the arrhythmogenic potential of drugs. Levo-bupivacaine has also a poor influence on QRS or corrected QT.[34]

We could not found any decrease in periferic oxygenation. This result was similar with the study of Glaser et al.[23] The increase in heart rate between postoperative first and third hours was

higher in Group - B. This result also supported that bupivacaine has more negative effects on haemodynamic parameters. However this does not prop up the result of the trial from Burke et al.[36]

The result of this study indicated that levobupivacaine-fentanyl and racemic bupivacaine-fentanyl show equally effective potencies for epidural analgesia. We aimed to obtain the effects of both solutions on systolic arterial blood pressure, diastolic arterial blood pressure, periferic oxygen saturation and analgesia. The rate of cardiac arrhythmia in the post-operative period is higher in Group-B. With regard to the safety of the S-isomer of bupivacaine, further clinical or experimental trials can be planned for different type of surgeries.

Conclusion

The results of our study suggest same concentration of epidural levobupivacaine and bupivacaine with fentanyl provide stable postoperative analgesia and both were found safe for the patients undergoing major abdominal surgery, but levobupivacaine is less tachycardic and safer for Type-2 Diabetic patient.

References:

1. Vadivelu N, Mitra S, Narayan D, Recent advances in postoperative pain management. Yale J Biol Med 2010:83(1):11-25.
2. Kampe S, Kiencke P, Delis A, Auweiler M, Konig DP, Kasper SM, The continuous epidural infusion of ropivacaine 0.1% with 0.5 microg x ml (-1) sufentanil provides effective postoperative analgesia after total hip replacement: a pilot study. Can J Anaesth 2003:50(6): 580-5.
3. Maheshwari AV, Blum YC, Shekhar L, Ranawat AS, Ranawat CS, Multimodal pain management after total hip and knee arthroplasty at the Ranawat Orthopaedic Center. ClinOrthopRelat Res 2009:467(6): 1418-23
4. Prakash S, Fatima T, Pawar M, Patient control analgesia with fentanyl for burn dressing changes. Anesth Analg 2004: 99(2): 552-5, table.
5. Mather LE, Chang DH, Cardiotoxicity with modern local anaesthetics: is there a safer choice? Drugs 2001: 61(3): 333-42.
6. Reiz S, Nath S, Cardiotoxicity of local anaesthetic agents. Br J Anaesth 1986: 58(7): 736-46
7. Hogan Q, Local anaesthetic toxicity: an update. Reg Anaesth 1996: 21(6 Suppl): 43-50
8. Davies, N.J.H & Cashman, J.N 2006, Lee's Synopsis of Anaesthesia,13th edition, Elsevier, India, p44-45.
9. Joel G. Hardman & Limbird, LE 1996, Goodman & Gilman's the Pharmacological Basis of Therapeutics, 9th edition, New York, McGraw-Hill, pp. 1762.
10. Weissman, C 1990, 'The metabolic response to stress. An overview and update', Anaesthesiology, vol. 73, pp. 308-27.
11. Rechcinska-Roslak B, Golebiowska J, Sibinski M, Synder M. Influence of surgical approach on the rehabilitation of patients after total knee arthroplasty. OrtopTraumatolRehabil 2010: 12(2): 136-43.
12. Ali M, Winter DC, Hanly AM, O'Hagan C, Keaveny J, Broe P, Prospective, randomized, controlled trial of thoracic epidural or patient-controlled opiate analgesia on perioperative quality of life. Br J Anaesth 2010: 104(3): 292-7.
13. Kopacz DJ, Allen HW,Thompson GE, A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg 2000: 90(3): 642-8.
14. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 2000: 59(3): 551-79.
15. Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg 1998: 86(4): 797-804
16. Bartha, E; Carlsson, P. & Kalman, S. (2006). Evaluation of costs and effects of epidural analgesia and patient-controlled intravenous analgesia after major abdominal surgery. British Journal of Anaesthesia, Vol.96, No. 1, (January 2006), pp. 111 – 117, ISSN 1471– 6771.

17. Block, B.; Liu, S. & Rowlingson, A. (2003). Efficacy of postoperative epidural analgesia: A meta-analysis. The Journal of the American Medical Association, Vol. 290, No.18, (November 2003), pp. 2455 – 2463, ISSN: 1538 – 3598.

18. Dolin, S.; Cashman, J. & Bland, J. (2002). Effectiveness of acute postoperative pain management: I. Evidence from published data. British Journal of Anaesthesia, Vol. 89, No. 3, (September 2002), pp. 409 – 423, ISSN 1471 – 6771.

19. Kehlet, H. (1997). Multimodal approach to control postoperative pathophysiology and rehabilitation. British Journal of Anaesthesia, Vol. 78, No. 5, (May 1997), pp. 606 – 617, ISSN 1471 – 6771.

20. Nimmo, S. (2004). Benefit and outcome after epidural analgesia. Continuing Education in Anaesthesia, Critical care & Pain, Vol. 4, No. 2, (April 2004), pp. 44 – 47, ISSN 1743 – 1824.

21. Wheatley, R.; Shug, S. & Watson, D. (2001). Safety and efficacy of postoperative epidural analgesia. British Journal of Anaesthesia, Vol. 87, No. 1, (June 2001), pp. 47 – 67, ISSN 1471 – 6771.

22. Waurick, R. & Van Aken, H. (2005). Update in thoracic epidural anaesthesia. Best practice & Research: Clinical Anaesthesia, vol. 19, No.2, (June 2005), pp.201 – 213, ISSN 1521 – 6896.

23. Albright G. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979; 51:285 – 7.

24. Huang Y, Pryor M, Mather L, Veering B, Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg 1998; 86:797 – 804.

25. Gristwood R, Bardsley H, Baker H, Dickens J. Reduced Cardiotoxicity of S(-)-bupivacaine compared with racemic bupivacaine(Marcaine) : new clinical evidence. Exp Opin Invest Drugs 1994; 3:1209 – 12.

26. Cox C, Checketts M, Mackenzie N, et al. Comparison of S (-)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. Br J Anaesth 1998; 80:594 – 8.

27. Cox C, Faccenda K, Gilhooly C, et al. Extradural S (-)-bupivacaine: comparison with racemic RS-bupivacaine. Br J Anaesth 1998; 80:289 – 93.

28. Liu S, Allen H, Olsson G. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards: prospective experience with 1,030 surgical patients. Anesthesiology 1998; 88:688 – 95.

29. Glaser C, Marhofer P, ZimpferG, Heinz MT, Sitzwohl C, Kapral S, et at. Levobupivacaine versus racemic bupivacaine for spinal anesthesia. Anesth Analg.2002; 94(1):194 – 8.

30. Bay-Nielsen M, Klarskov B, Bech K, Anderson J, Kehlet H. Levobupivacaine vs bupivacaine as infiltration anaesthesia in inguinal herniorrhaphy. Br j Anaesth. 1999; 82(2):280 – 2.

31. Cox CR, Checketts MR, Mackenzie N, Scott NB, Bannister J. Comparison of S(-)-bupivacaine with racemic(RS)-bupivacaine in supraventricular brachial plexus block. Br J Anaesth.1998; 80(5):594 – 8.

32. Cox CR, Faccenda KA, Gilhooly C, Bannister J, Scott NB, Morrison LM. Extradural S(-)-bupivacaine: Comperison with racemic RS-bupivacaine. Br J Anaesth. 1998; 80(3):289 – 93.

33. McGlade D, Kalpokas M, Mooney P, et al. Comperison of 0.5% ropivacaine and 0.55 bupivacaine in lumber epidural anaesthesia for lower limb orthopaedic surgery. Anaesth Intensive Care 1997; 25:262 – 6.

34. Wood M, Rubin A. Acomperison of epidural 1% ropivacaine and 0.75% bupivacaine for lower abdominal gynaecologic surgery. Anesth Analg 1993; 76:1274 – 8.

35. Mather L. Levobupivacaine: a viewpoint. Drug 1998; 56:363.

36. Wood MB, Rubin AP. A comparison of epidural 1% ropivacaine and 0.75% bupivacaine for lower abdominal gynecologic surgery. Anesth Analg. 1993; 76(6):1274 – 8.

37. Casati A, Ostroff R, Casimiro C, Faluhelyi A, Medina J, Fanelli G. 72-hour epidural infusion of 0.125% levobupivacaine following total knee replacement: a prospective, randomized, controlled, multicenter evaluation. Acta Biomed. 2008; 79(1):28 – 35.

38. Burke D, Kennedy S, Bannister J. Spinal anesthesia with 0.5% S(-)-bupivacaine for elective lower limb surgery. Reg Anesth Pain Med. 1999;24(6):519 – 23.

39. Ladd LA, Chang DH, Wilson KA, Copeland SE, Plummer JL, Mather LE. Effects of CNS site-directed carotid arterial infusions of bupivacaine, levobupivacaine, and ropivacaine in sheep. Anesthesiology. 2002; 97 (2): 418 – 28.

40. Fattorini F, Ricci Z, Rocco A, Romano R, Pascarella MA, Pinto G. Levobupivacaine versus racemic bupivacaine for spinal anaesthesia in orthopaedic major surgery. Minerva Anestesiol. 2006; 72(7 – 8): 637 – 44.

41. Breschan C, Jost R, Krumpholz R, Schaumberger F, Stettner H, Marhofer P, et al. A prospective study comparing the analgesic efficacy of levobupivacaine, ropivacaine and bupivacaine in pediatric patients undergoing caudal blockade. Paedia tr Anaesth. 2005; 15(4): 301-6.

42. Cox C, Faccenda K, Gilhooly C, et al. Extradural S(-)-bupivacaine: comparison with racemic RS-bupivacaine. Br J Anaesth 1998; 80:289 – 93.

43. Cox C, Checketts M, Mackenzie N, et al. Comparison of S (-)-bupivacaine with racemic (RS)-bupivacaine in supraclavicular brachial plexus block. Br J Anaesth 1998; 80:594 – 8.

44. Kehlet, H. & Holte, K. (2001). Effect of postoperative analgesia on surgical outcome. British Journal of Anaesthesia, Vol. 87, No. 1,(June 2001),pp. 62 – 72, ISSN 1471 – 6771.

45. Holte, K. & Kehlet, H. (2002).Epidural anaesthesia and analgesia – effects on surgical stress responses and implications for postoperative nutrition. Clinical Nutrition, Vol. 21, No. 3,(June 2002),pp. 199 – 206, ISSN 0261 – 5614.

46. Grass, J. (2000). The role of epidural anesthesia and analgesia in postoperative outcome. Anesthesiology Clinics of North America , Vol. 18, No. 2, (June 2000), pp. 407 – 428.

47. Wheatley, R.; Shug, S. & Watson, D. (2001). Safety and efficacy of postoperative epidural analgesia. British Journal of Anaesthesia, Vol. 87, No. 1, (June 2001), pp. 47 – 67, ISSN 1471 – 6771.

48. Kehlet, H. (2008). Fast –track colorectal surgery. The Lancet, Vol.371, No. 9615, (March 2008), pp. 791 – 793.

49. Kehlet, H. & Wilmore, D. (2008). Evidence – based surgical care and the evolution of fast-track surgery. Annals of Surgery, Vol. 248, No. 2, (August 2008), pp. 189 – 198, ISSN 1528 – 1140.

50. Carli, F.; Mayo, N. & Klubien, K. (2002). Epidural analgesia enhances functional exercise capacity and health related quality of life after colonic surgery: results of a randomized trial. Anesthesiology, Vol. 97, No. 3, (September 2002), pp. 540 – 549, ISSN 0003 – 3022.