European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 10, Issue 04, 2023

Original Research Article

A comparative study of equipotent doses of intrathecal clonidine and dexmedetomidine on characteristics of bupivacaine subarachnoid block

[1]Dr. Vaibhav Badsheshi, [2]Dr. Prashant S Karajgi, [3]Dr. Amitha, [4]Dr. Smita

[1]Assistant Professor, Department of Anesthesia, Shri B M Patil Medical College, Bldedu, Vijayapur, Karnataka, India
[2, 4]Assistant Professor, Mahadevappa Rampure Medical College, Gulbarga, Kalaburagi, Karnataka, India
[3]Assistant Professor, KBN Medical College, Kalaburagi, Karnataka, India

Corresponding Author:
Dr. Smita

Abstract

Introduction: As stated by Hippocrates - "Divine is the task to relieve pain"
Relief of pain during surgery is one of the components of balanced anaesthesia but this pain relief should be extended to the postoperative period also. According to Perkins and co-workers poorly managed acute pain like postoperative pain can lead to the occurrence of chronic pain.
Materials and Method: This clinical study was conducted on 156 adult patients of ASA physical status I to III in the age group of 18-60 years of either sex posted for elective lower abdominal or lower limb surgeries under spinal anaesthesia after taking informed consent at a tertiary hospital Vijayapur.
Results: Statistical tests used: anova, chi square test and tukey test.
Discussion: Spinal anaesthesia is currently wide spread popular anaesthetic technique available today. It has the definitive advantage that profound nerve block can be produced in a large part of the body by the relatively simple injection of a small amount of local anaesthetic.
Conclusion: Acute pain following surgical procedures is unique to the clinical practice of pain medicine. It is one of the few opportunities in which the cause of pain is known before its occurrence, the pain is reliably expected to occur and can be annulled effectively

Keywords: Comparative study, equipotent doses, clonidine, dexmedetomidine, bupivacaine.

Introduction

As stated by Hippocrates - "Divine is the task to relieve pain"
Relief of pain during surgery is one of the components of balanced anaesthesia but this pain relief should be extended to the postoperative period also. According to Perkins and co-workers poorly managed acute pain like postoperative pain can lead to the occurrence of chronic pain.[1] Postoperative pain relief is a growing concern for an anaesthesiologist as an uneventful postoperative period makes surgery a comfortable experience for surgical patients. Spinal anaesthesia was introduced into clinical practice by Karl August Bier in 1898. More than a century has passed and even today it is one of the most popular techniques for both elective and emergency surgical procedures particularly caesarean sections, lower abdominal surgeries, orthopaedic and urological surgeries just to name a few. Spinal anaesthesia is popular and commonly used worldwide. The advantages of an awake patient, minimal drug cost and rapid patient turnover has made this a method of choice for many surgical procedures. These advantages are sometimes offset by relatively short duration of action and

ISSN 2515-8260 Volume 10, Issue 04, 2023

complain of post operative pain. Spinal anaesthesia with hyperbaric Bupivacaine hydrochloride is popular for longer procedure due to its prolonged duration. But there is still a need to intensify and increase the duration of sensory block without increasing the intensity and duration of motor blockade and thus prolong the duration of post operative analgesia. Central neuraxial opioids, intrathecal as well as epidural offer the perceived benefit of selective analgesia without sensory or motor blockade. However side effects such as potentially catastrophic delayed respiratory depression have prompted further research to develop non opioid analgesics with lesser side effects. Intrathecal Clonidine is being extensively evaluated in last 25 years as an alternative to neuraxial opioids for control of pain and has proven to be a potent analgesic, free of at least some of the opioids related side effects.Unlike spinal opioids, Clonidine does not produce pruritis or respiratory depression. It also prolongs the necessary blockade and reduces the amount or concentration of local anaesthetic required to produce postoperative analgesia.

Aims and Objectives

To compare the following factors in 3 groups of 52 each
Group-B: 0.5% Bupivacaine 15mg + 0.5 ml Normal saline (Total volume 3.5ml)
Group-C: 0.5% Bupivacaine 15mg + 50 µg Clonidine (Test solution was diluted with Normal saline to a total volume of 3.5ml)
Group-D: 0.5% Bupivacaine 15mg + 5 µg Dexmedetomidine (Test solution was diluted with Normal saline to a total volume of 3.5ml)

With respect to
1. Sensory blockade- time to reach T10, time to peak sensory blockade, highest level of sensory block,
2. Motor blockade-time to reach Bromage scale 3.
3. Recovery parameter-Time to two segment regression, time to complete sensory and motor recovery (Bromage scale 0).
4. Analgesia – Duration of analgesia (the time of first rescue dose requested).
5. Intraoperative hemodynamic variations
6. Side effects

Materials and Method

This clinical study was conducted on 156 adult patients of ASA physical status I to III in the age group of 18years - 60 years of either sex posted for elective lower abdominal or lower limb surgeries under spinal anaesthesia after taking informed consent at a tertiary hospital Vijayapur.

Period of study: 18 Months (October 2013-june 2015)

Sample size

Estimation of sample size according to study by KANAZ GE et al, [8], The mean time of sensory regression to S1 segment was 303$\pm$75 Min in goup D(Dexmedetomidine), 272$\pm$38 Min in group C (Clonidine) 190$\pm$48 Min in group B(Normal Saline) The mean time of motor regression to bromage 0 was 250$\pm$76 Min in group D (Dexmedetomidine) 216$\pm$35 in group C (Clonidine) 163$\pm$47 in group B (Normal Saline) Considering the average mean and standard deviation of time of sensory regression and motor regression 287$\pm$56, at alpha error 0.05 and beta error 0.20 the sample size is 52 for each group respectively Following formula to be used to estimate the sample size for

$$n = \frac{(Z\alpha+Z\beta)^2 \times 2 \times S^2}{}$$

ISSN 2515-8260 Volume 10, Issue 04, 2023

d^2

Patients were randomly divided on an alternative basis into 3 groups of 52 each
Group-B: 0.5% Bupivacaine 15mg + 0.5 ml Normal saline (Test solution 3.5 ml)
Group-C: 0.5% Bupivacaine 15mg + 50 µg Clonidine (Test solution was diluted with Normal saline to a total volume of 3.5 ml)
Group-D: 0.5% Bupivacaine 15 mg + 5 µg Dexmedetomidine(Test solution was diluted with Normal saline to a total volume of 3.5 ml)

Inclusion Criteria

- Patients aged between 18-60 years
- ASA I-III
- Scheduled for elective lower abdomen and lower limb surgeries

Exclusion Criteria

- Patients using α_2-adrenergic receptors antagonists, calcium channel blockers, angiotensin converting enzyme inhibitors
- Dysrhythmia
- Body weight more than 120 Kg
- Height less than 140 cm,
- Post spinal surgeries, spinal deformity,
- History of allergy to study drugs,
- Pregnancy
- Coagulopathy
- Neurological disorder.

Observation and Results

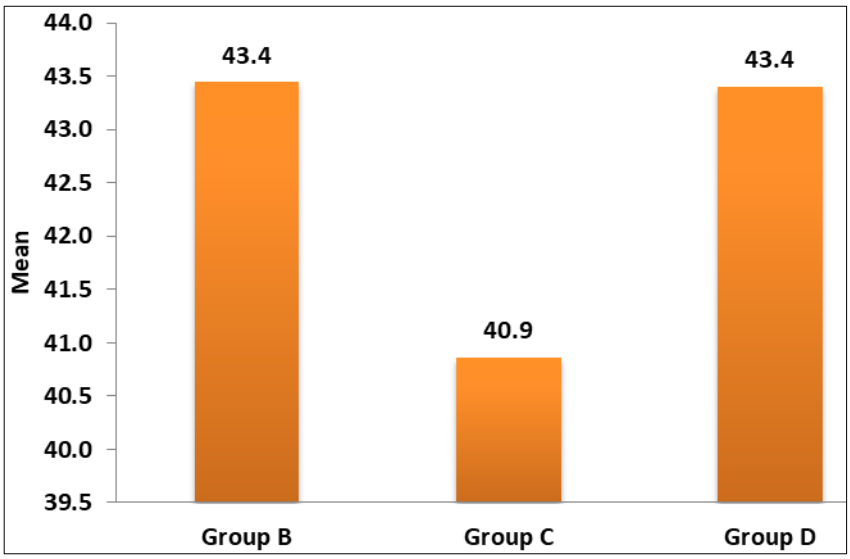
Table 1: Statistical tests used: anova, chi square test and tukey test demographic profile

		N	Mean	SD	p value
Age (Ys.)	Group B	43.4	9.4	43.4	0.271
	Group C	40.9	9.9	40.9	
	Group D	43.4	8.5	43.4	
	Total	42.6	9.3	42.6	
Hight (cm.)	Group B	159.9	4.0	159.9	0.789
	Group C	160.5	6.9	160.5	
	Group D	160.7	7.3	160.7	
	Total	160.3	6.2	160.3	
Weight (kg.)	Group B	57.6	6.2	57.6	0.732
	Group C	57.2	6.7	57.2	
	Group D	56.5	8.2	56.5	
	Total	57.1	7.1	57.1	

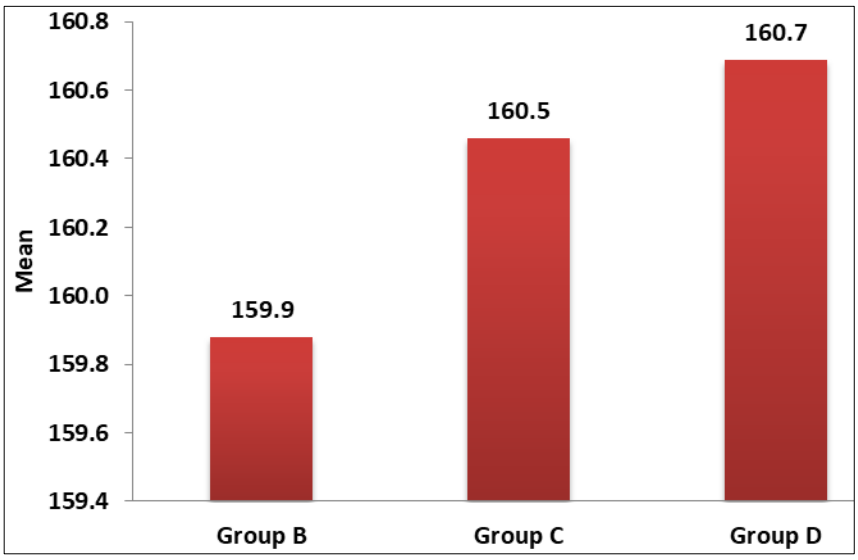
Values are expressed as Mean ±SD.

The mean age of the patient in group B was 43.4±9.4 years, in group c was 40.9±9.9 years and in group D was 43.4±8.5 years The mean height of the patient in centimetres in group B was 159.9 ±4.0, in group C was 160.5±6.9 and in group D was 160.7±7.3.The mean weight of the patient in kilograms in group B was 57.6 ± 6.2, in group C was 57.2± 6.7 and in group D was 56.5±8.2 kgs (Table 1). There was no statistically significant difference between the three groups with regards to age, height and weight (p>0.05).

ISSN 2515-8260 Volume 10, Issue 04, 2023



Graph 1: Mean distribution of Age (Yrs) among Study groups



Graph 2: Mean distribution of Height (cm.) among Study groups

Table 2: Gender distribution

Sex	Group B		Group C		Group D		Total		p value
	N	Percent	N	Percent	N	Percent	N	Percent	
Male	33	63.5	33	63.5	37	71.2	103	66	0.633
Female	19	36.5	19	36.5	15	28.8	53	34	

In group B, there were 33 males and 19 females, in group c there were 33 males and 19 females and in group D there were 37 males and 15 females. There was no statistically significant difference between the three groups in regard to sex. (p value >0.05)

Discussion

Spinal anaesthesia is currently wide spread popular anaesthetic technique available today. It has the definitive advantage that profound nerve block can be produced in a large part of the body by the relatively simple injection of a small amount of local anaesthetic [51]. An ideal local anaesthetic agent used in spinal anaesthesia in lower limb surgeries should have rapid onset of action, intense analgesia, adequate motor blockade, long duration of action, adequate postoperative analgesia though for limited duration and minimal cardiovascular changes. Bupivacaine introduced by "Ekenstam" in 1957 seems to fulfil most of the requirements of an

ideal local anaesthetic agent.

To address the problem of limited duration of action and to improve the quality of analgesia both intraoperative and postoperative, intrathecal opiates have been given in addition to Bupivacaine. However, this enthusiasm was soon tempered off by reports of side effects such as pruritis, urinary retention, nausea and vomiting and respiratory depression.

Although the endorphin system is well recognized, there are many other mechanisms involved in spinal antinociception and alpha$_2$ adrenergic agonists such as Clonidine and Dexmedetomidine have been shown to possess spinally mediated analgesic property. The mechanisms by which intrathecal α_2-adrenoceptor agonists prolong the motor and sensory block of local anaesthetics is not well understood. It is not a result of altered systemic absorption, as the plasma level of bupivacaine was not altered after the addition of intrathecal Clonidine to Bupivacaine spinal injection [52]. It may be an additive or synergistic effect secondary to the different mechanism of action local anaesthetic and the α_2-adrenoceptor agonist. The local anaesthetics act by blocking sodium channels, whereas the α_2-adrenoceptor agonist acts by binding to pre-synaptic C-fibres and post-synaptic dorsal horn neurons. Intrathecal α_2-adrenoceptor agonists produce analgesia by depressing the release of C-fibre transmitters and by hyperpolarisation of post-synaptic dorsal horn neurons [30, 53, 54, 55, 56]. This antinociceptive effect may explain the prolongation of the sensory block when added to spinal anaesthetics. On the other hand, Yaksh [57] has shown that intrathecal α_2-adrenoceptor agonists can cause a dose-dependent decrease in motor strength in animals. The prolongation of the motor block of spinal anaesthetics may result from the binding of α_2-adrenoceptor agonists to motor neurons in the dorsal horn [58]. Most of the clinical experience gained in the use of intrathecal α_2-adrenoceptor agonists has been described with Clonidine. The use of intrathecal Clonidine has a well-established synergistic effect with local anesthetic [7]. Using a combination of intrathecal Dexmedetomidine and local anaesthetics are lacking and off label.

Dosage selection

Kalso *et al*, [59] and Post *et al*, [60] showed that a 1 : 10 dose ratio between intrathecal Dexmedetomidine and Clonidine produced a similar effect in animal models. Asano *et al*, [61] showed that the potency of epidurally administered α_2-adrenoceptor agonists was well correlated with their binding affinity to spinal α_2-adrenoreceptors. The binding affinity of Dexmedetomidine compared with Clonidine is approximately 1: 10. Thus, it hypothesized that 3 µg of intrathecal Dexmedetomidine might be equipotent to 30 µg of intrathecal Clonidine. Several studies have been done using different doses of Clonidine (15-300 µg) and Dexmedetomidine in order to determine the most effective intrathecal administration with minimal side effects. In our study, 50µg of Clonidine and 5 µg of Dexmedetomidine were used, as it was found that the incidence of side effects increased with larger doses. In this clinical study, 156 patients in age group between 18-60 years, posted for various elective lower abdomen and lower limb surgeries belonging to ASA physical status I, II and III selected.

Group B: In this group, the patients received subarachnoid block with injection bupivacaine 0.5% (hyperbaric) 15 mg with added NS to make total volume of 3.5 ml.

Group C: In this group, the patients received subarachnoid block with injection bupivacaine0.5% (hyperbaric) 15 mg with 50µg Clonidine with added NS to make total volume of 3.5ml.

Group D: In this group, the patients received subarachnoid block with injection bupivacaine 0.5% (hyperbaric) 15 mg with 5 µg Dexmedetomidine (total volume of 3.5 ml).

Jorm *et al*, [62] found that Dexmedetomidine has an inhibitory effect on the locus coeruleus

ISSN 2515-8260 Volume 10, Issue 04, 2023

(A6 group) located at the brain stem. This supraspinal action could explain the prolongation of spinal anaesthesia after intravenous administration of Dexmedetomidine. The noradrenergic innervations of the spinal cord arises from the noradrenergic nuclei in the brain stem including the locus coeruleus, the A5, and the A7 noradrenergic nuclei. Neurons in the locus coeruleus are connected to the noradrenergic nuclei in the brain stem. Axon terminals of the noradrenergic nuclei reach lamina VII and VIII of the ventral horns of the spinal cord. The activity of the noradrenergic neurons is decreased by agonists acting at α2-adrenergic receptors on the locus ceruleus cell bodies. Therefore, inhibition of the locus coeruleus results in disinhibition of the noradrenergic nuclei and exerted descending inhibitory effect on nociception in the spinal cord [24].

Highest dose of intrathecal Dexmedetomidine used in animal studies was 100μg [51]. Konakci and colleagues [64] reported white matter injury in rats when high dose epidural Dexmedetomidine (6 μg/kg) was used alone;

However, subsequently Brummett and co-workers [65] demonstrated no injury and a protective effect when doses of 26-40 μg/kg were used perineurally. Although no major neurological complications have been reported so far, larger studies are required to rule out any short term or long term adverse effects.

Strebel and coworkers [66] compared three doses of Clonidine (37.5, 75, 150 μg) and concluded that Clonidine produced dose-dependent prolongation of the effects of intrathecal Bupivacaine.

In a study conducted by Hala E A Eid *et al*, [24] where Dexmedetomidine was used in combination with Bupivacaine in patients undergoing anterior cruciate ligament reconstruction surgery, Intrathecal Dexmedetomidine in doses of 10 μg and 15 μg significantly prolong the anaesthetic and analgesic effects of spinal hyperbaric Bupivacaine in a dose-dependent manner.

We compared the onset and duration of sensory and motor block, hemodynamic effect and adverse effects of Dexmedetomidine or Clonidine given intrathecally with hyperbaric 0.5% Bupivacaine for lower abdomen and lower limb surgeries. In this clinical study, 156 patients in age group between 20-60 years, posted for various elective lower abdomen and lower limb surgeries belonging to ASA physical status I, II and III selected.

Group B: In this group, the patients received subarachnoid block with injection Bupivacaine 0.5% (hyperbaric) 15 mg with added NS to make total volume of 3.5ml.

Group C: In this group, the patients received subarachnoid block with injection Bupivacaine0.5% (hyperbaric) 15 mg with 50μg Clonidine with added NS to make total volume of 3.5ml.

Group D: In this group, the patients received subarachnoid block with injection bupivacaine 0.5% (hyperbaric) 15 mg with 5 μg Dexmedetomidine (total volume 3.5ml).

Demographic profile

The mean age of the patient in group B was 43.4±9.4 years, in group C was 40.9±9.9 years and in group D was 43.4±8.5 years The mean height of the patient in centimetres in groupB was 159.9 ±4.0, in group C was 160.5±6.9 and in group D was 160.7±7.3.The mean weight of the patient in kilograms in groupB was 57.6 ± 6.2, in groupC was 57.2± 6.7 and in group D was 56.5±8.2 kgs (Table 1). There was no statistically significant difference between the three groups with regards to age, height and weight (p>0.05).

Gender Distribution

In group B, there were 33 males and 19 females, in group c there were 33 males and 19 females and in group D there were 37 males and 15 females. There was no statistically significant difference between the three groups in regard to sex. (p value >0.05)

ISSN 2515-8260 Volume 10, Issue 04, 2023

Conclusion

Acute pain following surgical procedures is unique to the clinical practice of pain medicine. It is one of the few opportunities in which the cause of pain is known before its occurrence, the pain is reliably expected to occur and can be annulled effectively.
Despite advances in the knowledge of pathophysiology, pharmacology and the development of more effective techniques for the management of perioperative analgesia, many patients continue to experience distressing pain in the postoperative period. It is shown that relief of pain with neuraxial blockade with a local anaesthetic like Bupivacaine alone is limited to the initial postoperative period. When a combination of local anaesthetic and an alpha $_2$ adrenergic agonist like Clonidine is used, pain relief can be extended well into the post operative period. In conclusion, this study shows that the supplementation of bupivacaine spinal block with a low dose of intrathecal Dexmedetomidine (5 µg) or Clonidine (50 µg) produces a significantly shorter onset of motor and sensory block and a significantly longer sensory and motor block than bupivacaine alone. The 50µg of Clonidine or 5 µg of Dexmedetomidine dose provides maximum benefit and minimum side effects. These doses have an effect on sedation level, heart rate and mean arterial pressure which does not however require any therapeutic intervention and hence can be advocated as an adjuvant to bupivacaine in spinal anaesthesia for lower abdomen and lower limb surgeries. This approach to pain therapy may hold promise, that favourable outcomes such as successful analgesia may be achieved with minimal side effects.

Summary

Spinal anaesthesia is effective in the management of perioperative pain which extends into the initial post operative period. In order to maximize post operative pain free period numerous techniques and newer drugs have been tried.
In this study, the anaesthetic properties of 15 mg of 0.5% hyperbaric Bupivacaine, 15 mg of 0.5% hyperbaric bupivacaine with 50 µg of Clonidine and 15 mg of 0.5% hyperbaric Bupivacaine with 5µg of Dexmedetomidine given intrathecally were compared.
One hundred and fifty six patients ASA physical status I, II and III patients, posted for various elective lower abdomen and lower limb surgeries were studied.
The patients were divided into three groups of 52 each:

Group B: Received 0.5% hyperbaric bupivacaine 15 mg + NS 0.5 ml

Group C: Received 0.5% hyperbaric bupivacaine 15 mg + 50 µg of Clonidine.(total volume 3.5 ml with NS)

Group D: Received 0.5% hyperbaric bupivacaine 15 mg + 5µg of Dexmedetomidine (total volume 3.5 ml with NS)
Addition of 50 µg of Clonidine and 5µg of Dexmedetomidine to hyperbaric bupivacaine resulted in a statistically significant faster onset of the motor blockade The time to reach bromage scale 03 was (15.0±3.4 min. in Group B, 9.6±2.0 min. in Group C and 10.5±1.6 min. in Group D). P value was < 0.001 (statistically significant). It was fastest in group C followed by group D and last was group B.
The time required to reach T10 sensory block level was shorter in group C and D as compared to group B (Mean time required to reach T10 sensory block level was 5.8±2.1 min. In Group B, 5.6±1.4 min. in Group C and 6.3±1.1 min. in Group D. P value was< 0.001 (statistically insignificant).
Intergroup comparison B to C and B to D P value was insignificant (less than 0.05).Whereas C to D was not significant > 0.05
The maximum level of sensory block achieved was shorter but it was statistically insignificant (mean time to reach peak sensory block level 14.6±4.0 min. in Group C and

ISSN 2515-8260 Volume 10, Issue 04, 2023

16.0±4.0min. in Group D as compared to 15.5±3.2 min. in Group B).
Time for 2 segment regression was significantly prolonged in Group C and Group D ($p<$ .001) with a mean duration of 120.70±29.5. Min. in Group C and 140.4±29.30 min. in Group D as compared to 96.9±27.9 min. in Group B and was found to be statistically significant.
Intergroup comparison B to C, B to D and C to D was significant (less than 0.05).It was longest in group D followed by group C and B.
The time to regression time to S1 dermatome was 195.1± 30.30 min. in Group B, 274.4± 26.50 min. in Group C and 302.40±49.60 min. in Group D. P value was < 0.001 (statistically significant).Compete recovery of sensory function was observed in all studied patients.
Intergroup comparison B to C, B to D and C to D was significant (P less than 0.05).It was longest in group D followed by group C and than group B.
We found that duration of analgesia was significantly prolonged in Group C and Group D ($p<$ .001) with a mean duration of 257.1±49.0 min. in Group B, 488.3±56.3 min. in Group C and 612.3±77.0 min.
Intergroup comparison B to C, B to D and group C to D was significant (less than 0.05).Duration was longest in group D followed by group C and than group B.
With the above findings it is evident that the use of 50 µg of Clonidine and 5µg of Dexmedetomidine as an adjuvant to hyperbaric bupivacaine in lower abdomen and lower limb surgeries is beneficial in several aspects (shorter onset of motor and sensory block and longer sensory and motor block) without any significant hemodynamic instability. And scored over the use of hyperbaric bupivacaine alone with minimal side effects.

References

1. Rowling JC. Chronic Pain, Chapter 73 in Millers‘ Anaesthesia, Sixth Edition, Elsevier Churchill Livingstone. 2004;2763-2784.
2. Vaswani RK, Raiger LK, Purohit R, Bajaj P. The effect of intrathecal midazolam on postoperative pain relief in orthopaedic surgery. Hospital Today. 2002;7(4):150-153.
3. Parameshwara G. spinal,epidural to combined spinal epidural analgesia,the history of central neuraxial block. Indian J Anaesth. 45(6):406-412.
4. Dureja GP, Jayalaxmi TS. Colloid preloading before spinal and epidural anaesthesia. Hospital today. 2000:V(11):601-603.
5. Gustafsson LL, Schildt B, Jackobson K. Adverse effects of extradural and intrathecal opiates; Report of a nationwide survey in Sweden.Br J Anaesth. 1982;54;479-86.