To assess the efficacy of verapamil 5mg as an adjuvant to 0.5% plain Bupivacaine in Lumbar Epidural Anaesthesia for elective inguinal surgeries in comparison with 0.5% plain Bupivacaine

Dr D.Senthil Kumar,Dr Santha arulmozhi.K
Coimbatore Medical College

Abstract: *Pain is an unpleasant sensation which is almost totally subjective. It is a physiologically protective mechanism, but in excess, it becomes destructive and even fatal. Pain is the result of sensory perception and cortical integration of the stimuli that threaten the integrity of the body tissues.The International Association for the Study of Pain defines pain as an \"unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage\".An ideal technique should provide effective pain relief with minimal side effects and a reasonable level of patient satisfaction in the post operative period. Epidural analgesia is one of the entities practised to provide post operative pain relief. Central neuraxial blockade with a \"combination therapy\" of local anaesthetics and non opiates yield near total pain relief while diminishing or avoiding side effects from each component alone. This newer dimension in pain management can be called balanced epidural analgesia. It offers the most complete form of analgesia. This study was undertaken to assess the efficacy of verapamil 5mg as an adjuvant to 0.5% plain Bupivacaine and found that epidural bupivacaine (0.5%) with verapamil prolonged the postoperative analgesic period when compared to 0.5% bupivacaine alone for elective inguinal herniorraphy surgeries under lumbar epidural anaesthesia.*

I. Introduction

Pain is an unpleasant sensation which is almost totally subjective. It is a physiologically protective mechanism, but in excess, it becomes destructive and even fatal. Pain is the result of sensory perception and cortical integration of the stimuli that threaten the integrity of the body tissues.

The International Association for the Study of Pain defines pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".

The perception of pain has two main components:
1. The original sensation (in response to stimuli)
2. The reaction or processing component.
Post operative pain lies between these two modalities.

An ideal technique should provide effective pain relief with minimal side effects and a reasonable level of patient satisfaction in the post operative period. Epidural analgesia is one of the entities practised to provide post operative pain relief.

Central neuraxial blockade with a "combination therapy" of local anaesthetics and non opiates yield near total pain relief while diminishing or avoiding side effects from each component alone. This newer dimension in pain management can be called balanced epidural analgesia. It offers the most complete form of analgesia.

Local anaesthetics may be used alone or in combination with opiates or non opiates epidurally to prevent pain and attenuate the stress response intra operatively and to provide good post operative pain relief.

Bupivacaine has traditionally been the longest acting local anaesthetic commercially available and widely used. Its prolonged duration of action reduces the need for repeated administration of top up doses. Furthermore, Bupivacaine has a differential sensory to motor blockade. This is important for its use in post operative pain relief.

The primary mode of action of local anaesthetics is through sodium channel and axonal conduction blockade. Local anaesthetics also have extensive effects on presynaptic calcium channels that must function to stimulate the release of neurotransmitters. Thus interference with calcium channel conductance may enhance epidural anaesthesia with local anaesthetics.

Excitatory aminoacids involved in nociceptive transmission in the dorsal horn of the spinal cord are mediated by N-methyl D-aspartate receptors (NMDA). Activation of NMDA receptors leads to Ca^{2+} entry into the cell and initiates a series of Central sensitization. This central sensitization may be prevented by calcium channel blockers that block calcium entry into the cell.

This study is aimed at adding verapamil, a L-type calcium channel blocker to epidural Bupivacaine, to improve

quality of analgesia and prolong the post operative period of analgesia in patients undergoing herniorraphy.

Aim of The Study

This study was undertaken to assess the efficacy of verapamil 5mg as an adjuvant to 0.5% plain Bupivacaine in Lumbar Epidural Anaesthesia for elective inguinal surgeries in comparison with 0.5% plain Bupivacaine with regard to the following parameters:

1. Time of Onset
2. Duration of analgesia
3. Hemodynamic changes
4. Respiratory changes
5. Level of sensory blockade
6. Quality of motor blockade
7. Complications

II. Materials And Methods

This study was done at Coimbatore medical college hospital , Coimbatore. The aim of this study was to assess the efficacy of Verapamil –5mg as an adjuvant to 0.5% Bupivacaine in Lumbar Epidural Anaesthesia for elective inguinal herniorraphy surgeries.

Study Design

This study is a randomized, prospective, double blinded study.

Inclusion Criteria

40 Patients of ASA grade I or grade II between the age group of 20-50 years scheduled for herniorraphy surgeries were included in the study. The patients were assigned to two groups. Group I received 16 ml of 0.5% Bupivacaine with 2ml of normal saline. Group II received 16 ml of 0.5% Bupivacaine with 2 ml of Verapamil (5 mg).

Exclusion Criteria

• Patients not willing for regional anaesthesia
• ASA Grade III/ Grade IV patients
• Patients with cardiac disease
• Patients with neurological illness
• Patients with impaired hepatic function
• Patients with impaired renal function
• Spine deformity
• Local sepsis
• Bleeding disorders
• Technical failure - Dural tap, Bloody tap.
• Any H/O allergy
• Hearing impairment

Consent

The Institutional Ethics Committee approval and the patients informed consent were obtained prior to the study.

Pre Operative Visit

A careful history and physical examination of the patient was done.
The following routine preoperative investigations were assessed :

Blood : Haemoglobin%Total countDifferential countErythrocyte Sedimentation rateBlood grouping and typingBleeding Time an Clottingtime Blood-urea, sugarSerum Creatinine Liver function tests
Urine : Albumin, Sugar
Chest : X-ray ECG

Patients vital signs and weight were noted down. Patients were taught about the visual analogue scale during the pre-operative visit. Here the patients were shown a 100 mm scale and it was explained to them that the

score of 0 meant no pain and the score of 100 meant worst possible pain that can be imagined.
Pre operative fasting of 6 hours for solid food and 4 hours for clear liquid was advised.

Premedication
No premedication was prescribed during the pre-anaesthetic evaluation.

Lumbar Epidural Block
On the day of surgery after the pre-operative examination, the patient was shifted to the operating room and an ECG monitor, non invasive blood pressure and pulseoximeter were connected. Base line heart rate, blood pressure and oxygen saturation were noted.

Patients was preloaded with 10ml/kg body weight of Ringer Lactate solution using a 16 gauge iv Cannula. Local anaesthetic samples were prepared by an anaesthesiologist who was not involved in the clinical study. The observer was not aware of the type of local anaesthetic in each preparation.

Patient was then positioned in the right lateral position. The Thoraco lumbar area was thoroughly cleaned with Povidone-Iodine solution and sterile drapes were placed around the site. Skin and subcutaneous tissue infiltration with 0.5-1ml of 1% lignocaine was done at the L3 L4 level using a 26 gauge needle. A 16 Gauge size Tuohy needle was introduced into the lumbar epidural space through the mid line approach. The extradural space was identified using a loss of resistance to air technique with a 5ml syringe. A standard 18G epidural catheter was threaded into the epidural space. Four cm of the catheter was advanced cephalad into the space.

A test dose of 0.5% bupivacaine 1 ml with adrenaline 1: 200,000 was injected after negative aspiration for CSF or blood through epidural catheter. The total calculated dose of local anaesthetic solution was then injected 3 mins after the test dose if there was no significant change in the heart rate or arterial pressure. The case was excluded from the study if there was any significant change in the heart rate subsequent to the test dose.
The patient was turned from the lateral to the supine position. Spo_2 and ECG were monitored throughout the procedure, intraoperatively and post operatively. Heart rate, blood pressure and respiratory rate were recorded every 5 mins for the first 30 mins, every 15 mins for next 30 mins. every 30 mins for next 2 hours and every hour for next 3 hours.

Onset of Sensory Analgesia
It was noted as the time taken for the disappearance of pinprick pain from the administration of local anaesthetics into the epidural space, at the puncture dermatomal level.

Maximum Level of Sensory Blockade
It was taken to be the upper level of absence to pinprick pain 20 mins after the epidural injection.

Duration of Sensory Analgesia
Sensory analgesia was assessed as per visual analogue scale scoring at 2,4,6,12, 24 hours post operatively. Rescue analgesia was given by injecting 6 to 8 ml of 0.25% bupivacaine at VAS 4 through the catheter.
The duration of sensory analgesia is calculated from the time of administration of local anaesthetic drug till the time rescue analgesia is sought.

Assessment of Motor Blockade

Motor blockade was assessed using Bromage scale

Score	Motor block		
0	0%	Nil	Free movement of legs and feet
1	33%	partial	Just able to flex knees free movement of feet
2	66%	Almost complete	Unable to flex kneesfree movement of feet
3	100%	complete	Unable to move legs or feet

The scores were recorded every 15 mins after the epidural injection till a score of 0 was obtained.

Duration of Surgery
It was the time from skin incision to the end of surgery.

Complications
Post operatively patients were observed for
• Nausea, vomiting
• Respiratory depression
• Hypotension (drop of more than 25% from the base line)

- Bradycardia (equal to or less than 60/mt)
- Urinary retention
- SpO_2 decrease (below 90%)
- Shivering
- Arrhythmias
- Conduction defects
- Pain at injection site

III.   Observation And Results

This study was conducted on forty patients undergoing elective herniorraphy surgeries. The observations were recorded during the intra operative and the post operative period. All these patients were grouped in to two categories.

Group I : Patients who had received 16 ml of 0.5% Bupivacaine + 2 ml of normal saline

Group II : Patients who had received 16 ml of 0.5% Bupivacaine + 2 ml of Verapamil (5 mg).

Patients Characteristics

In Group I there were 20 male patients and in Group II there were 20 male patients.

Table 1 Age (In Years)

Group	Mean age(in years)	± SD	t-test	P value	Statistical Significance
Group I	32.80	5.85	0.11	0.9146	NS
Group II	33.00	5.87			

NS: Not Significant

The mean age in Group I was found to be 32.80 ± 5.85 years and the mean age in Group II was found to be 33.00 ± 5.87 years.

Table 2 Weight (In Kgs)

Group	Mean weight in Kgs	± SD	t-test	P value	Statistical Significance
Group I	55.25	4.41	1.01	0.3196	NS
Group II	54.00	3.36			

NS: Not Significant

The mean weight in Group I was 55.25 ± 4.41 kgs and in Group II was 54.00 ± 3.36 kgs.

Table 3
Height (In Cms)

Group	Mean height in Cms	± SD	t-test	P value	Statistical Significance
Group I	156.70	2.89	1.95	0.0584	NS
Group II	159.20	4.95			

NS : Not Significant

The mean height in Group I was 156.70 ± 2.89 cms and in Group II was 159.20 ± 4.95 cms.

Table 4
Sex Distribution

Group	Males	Females
Group I	20	-
Group II	20	-

NS : Not Significant

The distribution of age, weight, height and the sex of patients in both the groups were similar and comparable.

Table 5
Pulse Rate (Beats/Minute)

Group	Mean pulse rate (Beats/min)	SD	t-test	P value	Statistical Significance
Group I	77.96	4.13	1.52	0.1648	NS
Group II	78.95	5.05			

NS : Not Significant

The mean pulse rate in Group I was found to be 77.96 /mt with standard deviation of 4.13. The mean pulse rate in Group II was found to be 78.95 /mt with standard deviation of 5.05.

Table 6
Respiratory Rate (nos/min)

Group	Mean respiratory rate (nos/min.)	± SD	t-test	P value	Statistical Significance
Group I	14.24	1.85	1.18	0.3326	NS
Group II	14.70	1.93			

NS : Not Significant

The mean respiratory rate in Group I was found to be 14.24 / mt with SD of 1.85. The mean respiratory rate in Group II was found to be 14.70 / mt with SD of 1.93.

Table 7
Systolic Blood Pressure (In Mm Of Hg)

Group	Mean systolicBP (in mm of mg)	± SD	t-test	P value	Statistical ignificance
Group I	114.47	7.30	0.76	0.5458	NS
Group II	113.93	7.16			

NS : Not Significant

The mean Systolic BP in Group I was found to be 114.47 mmHg with SD of 7.30 mmHg. The mean systolic BP in Group II was found to be 113.93 mmHg with SD of 7.16 mmHg.

Table 8
DIASTOLIC BLOOD PRESSURE (in mm of Hg)

Group	Mean diastolic BP (in mm of Hg)	± SD	t-test	P value	Statistical Significance
Group I	73.88	5.21	0.78	0.4954	NS
Group II	74.33	5.17			

NS : Not Significant

The mean Diastolic BP in Group I was found to be 73.88 mmHg with SD of 5.214 mmHg. The mean Diastolic BP in Group II was found to be 74.33 mmHg with SD of 5.17 mmHg.

The difference in mean pulse rate, respiratory rate, systolic blood pressure and diastolic blood pressure were not statistically significant and were comparable.
The Heart Rate, Respiratory Rate and Blood Pressue were recorded every 5 mins. of first 30 mins. after epidural injection every 15 mins till 1 hour and every 30 mins. there after.
There was no significant differences in heart rate between Group I and Group II. Through out the intraoperative and post operative period the blood pressure was similar in both groups.

Onset Of Analgesia

Table 9
Onset Of Analgesia (In Minutes)

Group	Mean onset of analgesia(in minutes)	± SD	t-test	P value	Statistical Significance
Group I	16.90	2.49	0.27	0.7892	NS
Group II	17.10	2.20			

NS : Not Significant

The mean onset of analgesia for Group I was 16.90 ± 2.49 mins and for Group II 17.10 mins ± 2.20. The mean time to onset of action in both the groups were statistifically not significantly different.

Maximum Sensory Level

Table 10
Maximum Sensory Level(Segments)

Group	Mean maximum sensory level (segments)	± SD	t-test	P value	Statistical Significance
Group I	T 6.80	0.77	0.60	0.5554	NS
Group II	T 6.95	0.83			

NS : Not Significant

The mean maximum sensory level in Group I was found to be 6.80 ± 0.77. The mean maximum sensory level in Group II was found to be 6.95 ± 0.83. This is also not significantly different.

Maximum Motor Blockade
Table 11
Maximum Motor Block (According To Bromage Scale)

Group	Mean maximum motor block	± SD	t-test	P value	Statistical Significance
Group I	2.50	0.51	0.31	0.7590	NS
Group II	2.55	0.51			

NS : Not Significant

The mean maximum Motor blackade in Group I was found to be 2.50 ± 0.51. The mean maximum Motor blackade in Group II was found to be 2.55 ± 0.51. This was also Not significantly different.**The sensory level and motor blockade were statistically Not significantly different in the 2 groups**.

Duration Of Surgery

Table 12
Duration Of Surgery (In Minutes)

Group	Mean duration of surgery (in minutes)	± SD	t-test	P value	Statistical Significance
Group I	92.85	5.07	0.58	0.5663	NS
Group II	91.90	5.31			

NS : Not Significant

The mean duration of surgery in Group I was found to be 92.85 ± 5.07 mins. The mean duration of surgery in Group II was found to be 91.90 ± 5.31 mins. The mean duration of surgery is not statistically significantly different.

Duration Of Analgesia

Table 13
Duration Of Analgesia (In Minutes)

Group	Mean duration of analgesia (in minutes)	± SD	t-test	P value	Statistical Significance
Group I	175.70	13.21	16.13	0.000	**S-Significant**
Group II	323.20	38.71			

S : Significant
In Group I the patients who have received only epidural Bupivacaine, the mean duration of analgesia was 175.70 mins. with SD of 13.21 i.e. around 3 hrs.
In Group II the patients who have received Bupivacaine with verapamil, the mean duration of analgesia was 323.20 with SD of 38.71 i.e. around 6 hours.
Duration of analgesia was found to be significantly different. In the verapamil group the duration of analgesia was prolonged and the requirement of post operative analgesics was reduced.

Spo$_2$
SpO$_2$ was maintained in both the groups between 96 to 99%. No patients needed supplemental oxygenation.

Complications
There was no incidence of complications like
• 　　Nausea

- Vomiting
- Retention of urine
- Hypotension (25% below the baseline level)
- Brady cardia (Rate less than 60/min.)
- AV conduction defects or arrhythmias,
- Pruritis
- Respiratory depression (less than 8/mt).

IV.   Discussion

Providing intra operative pain relief is the "raison –d- etae" of anaesthesia. It would be advantageas if this pain relief could be extended into the post operative period as well. The prevention of pain is much simpler to achieve than the treatment of pain once established. Epidural analgesia is the presently favoured method to provide intra operative and post operative analgesia.

Epidural anaesthesia and analgesia have been evolved now with novel analgesic agents. Opioids, Ketamine, Clonidine, neostigmine, adenosine, midazolam and tramadol are now being used as adjuvants with local anaesthetics to provide pain relief by epidural administration. These adjuvants provide more potent action in reducing pain and in prolonging post operative analgesia.

Recent studies show that calcium channel blockers like verapamil can also be used to provide pain relief. Normal calcium movement is essential for normal sensory processing. A disruption of calcium influx will interfere with normal sensory processing, thus contributing to reduced pain. Inhibition of calcium influx by calcium channel blockers produces antinociception at the level of the spinal cord.

In this study, epidural administration of bupivacaine and verapamil in herniorraphy surgeries produced effective analgesia and increased the post operative duration of analgesia.

All patients suffering from cardiac illness had been excluded. P.Foex say that the rate of sinus node discharge is depressed and atrioventricular time is prolonged by verapamil. Myocadial contractility decreases in a dose dependent fashion. Patients who are recieving betablockers for cardiac illness or anxiety or Hyperthyroidism, were carefully excluded from our study. The concomittant use of verapamil and betablockers may potentiate negative ionotropy, chronotropy and dromotropy.

Preoperative and Post operative 12 lead ECG were recorded. Intraoperative ECG monitoring was done as verapamil may produce conduction abnormalities like prolongation of PR interval. Non-invasive blood pressure and pulseoximeter were connected. Baseline heart rate, blood pressure and oxygen saturation were noted.

Our study concurs with the double blind study done by Huhnchoe, Jin song kim, Seong Hoon Ko, Young chin Han, He -Sun song on how epidural verapamil reduces analgesic consumption after lower abdominal surgery during the Post operative period.

The patients selected for our study were exclusively male patients undergoing inguinal herniorraphy surgeries for the purpose of uniformity. The age, weight and height were also similar and comparable so that the study of the level of sensory blockade should not be affected in our study.

Kapur *et al.,* 1984 say a verapamil and Fentanyl combination produced marked vasodilation. As Kapur stated, opiates for premedication were prevented. No premedication was given in our study as it may in influence the heart rate, duration of analgesia and haemodynamic changes.

At present pain during the intra operative and post operative period are of more concern. B.L. Kidd and L.A. Urban say that nociception may be defined as the detection of noxious stimuli and the subsequent transmission of encoded information to the brain. The responses to noxious stimuli may be enhanced (hyperalgesia) or normally innocuous stimuli may produce pain (allodynia). This pain will stimulate the sympathetic nervous system after surgical incision and produce an increase in pulse rate and blood pressure. This increase in heart rate leads to increased myocardial oxygen consumption. In both the groups of our study, we experienced neither tachycardia nor Hypertension due to an adequate epidural blockade.

Purnel RJ 1985 in his study demonstrated bradycardia after verapamil and spinal analgesia. The total incidence of bradycardia (ventricular rate less than 50 beats/minute) was 1.4%, in controlled studies, through IV administration of verapamil. Verapamil did not produce significant bradycardia in ideal dosages. As in both the groups, the maximum level of sensory blockade was only at T6 to T7 level bradycardia was not experienced. The mean pulse rate in Group I (0.5% bupivacaine alone) was found to be 77.96 ± 4.13/min and in Group II (0.5% bupivacaine + 5 mg of verapamil) was found to be 78.95 ± 5.05/min. Verapamil is a much less powerful vasodilator than nifedipine and therefore causes less reflex increase in ß adrenoreptor activity. It reduces peripheral vascular resistance usually without reflex tachycardia. So undue tachycardia was not seen.

Due to pain, the respiratory rate will increase. The tidal volume to perfusion ratio will reduce and may result in hypoxeamia. In our study the mean respiratory rate in Group I (0.5% bupivacaine alone) was found to be

14.24 ± 1.85 and Group II (0.5% bupivacaine + 5 mg of verapamil) was found to be 14.70 ± 1.93. The shows the adequacy of blockade produced by epidural bupivacaine and verapamil.

Verapamil is a potent smooth muscle relaxant with vasodilatory properties, as well as a depressant of myocardial contractility and these effects are largely independent of autonomic influences. It reduces peripheral vascular resistance without reflex tachycardia. Epidural verapamil did not produce hypotension. The mean systolic pressure in Group II (0.5% bupivacaine + 5 mg of verapamil) was 113.93 ± 7.16 mm of Hg and the mean diastolic pressure was 74.33 ± 5.17 mm of Hg. The maximum sensory level in both the groups were between T6 to T7 level. So neither hypotension nor bradycardia was seen.

Onset of sensory analgesia and Motor blockade was neither prolonged nor reduced by addition of verapamil epidurally to bupivacaine. The onset of analgesia in Group I (0.5% bupivacaine alone) was found to be 16.90 ± 2.49 mins and Group II (0.5% bupivacaine + 5 mg of verapamil) was found to be 17.10 ± 2.20 minutes. The motor blockade in Group I (0.5% bupivacaine alone) was 2.50 ± 0.51 and Group II (0.5% bupivacaine + 5 mg of verapamil) was found to be 2.55 ± 0.51 according to the bromage scale.

Since we had selected inguinal herniorraphy surgery for our study, we did not find major differences in the duration of surgery.

Addition of verapamil to bupivacaine in epidural administration had a significant influence on the duration of analgesia. The duration of analgesia in Group II (0.5% bupivacaine + 5 mg of verapamil) was 323.20 ± 38.71 minutes i.e around 6 hours. The duration of analgesia is Group I (0.5% bupivacaine alone) was 175.70 ± 13.21 minutes i.e around 3 hours. The mean duration of surgery in Group I and Group II was around one and a half hours. Addition of 5 mg of verapamil to 0.5% bupivacaine had produced post operative analgesia for four and half hours where as Group I (0.5% bupivacaine alone) had produced post operative analgesia for one and a half hours. These results simulate the study done by Huhn Choe and Jin-song Kim, in which they say that post operative analgesic consumption was less by the addition of verapamil to 0.5% bupivacaine.

Many studies have been done to demonstrate the usage of verapamil with local anaesthetics spinally and epidurally to produce antinociception. Himes, Difacio and Burney 1977 say verapamil causes some blockade of sodium channels also. Iwasaki H, Omote K, Kavamata M 1995 says that sensory blockade produced by lignocaine is potentiated by calcium channel blockers. They also demonstrated in rats that local sensory block produce by lignocaine injection at its tail base was potentiated by verapamil in a dose dependent manner.

Hara K and Saito Y evaluated the effects of verapamil on somatic and visceral nociception at the level of the spinal cord. In Sprague-Dawley rats 50 μgms of verapamil injected, with isotonic normal saline as control in to the intrathecal lumbar catheters. Intrathecally administered verapamil increased both tailflick latency and colorectal distension threshold where as isotonic normal saline does not. This indicates verapamil produced both somatic and viseral nociception. It suggests a possible clinical application of verapamil to pain.

Bingurann D, Lipinski HG, Hagemann G, Speckmann 1990 concluded in their study that local anaesthetics block sodium channels primarily from the intracellular side. The primary mode of action of Local anaesthetics is through sodium channel and axonal conduction blockade. It also has extensive effects on presynaptic calcium channels that must function to stimulate the release of neurotransmitters. Thus if we add verapamil and interfere with calcium conductance it may enhance epidural anaesthesia with local anaesthetics due to its synergistic effect.

Omote K, Iwasaki 1995 investigated the effects of intrathecal verapamil on spinal anaesthesia with local anaesthetics. Male Sprague Dawley rats were chronically implanted with Lumbar intrathecal catheters. Tail flick and mechanical paw pressure tests were used to assess thermal and mechanical pain threshold respectively. Motor function was assessed through modified Langerman's scale. Intrathecal lidocaine showed prolongation of tail flick latency i.e. thermal threshold, increase in mechanical paw pressure i.e. mechanical threshold and increase in motor function. Intrathecal verapamil alone (50-200 microgram) did not produce sensory or motor block. When combination of 50 μgm of verapamil and 200 μgm of lidocaine produced more potent and prolonged antinociception and motor blockade. Their study indicate that intrathecal verapamil potentiates spinal anaesthesia with local anesthetics. Thus epidural Ca^{2+} channel blockers potentiate the analgesic effects of local anaesthetics. Toxic doses of local anaesthetics can be reduced and may be used synergistically for clinical pain management by adding verapamil.

Wong CH, Dey P. 1994, Department of Anaesthesiology, New Jersey Medical School, New York explored the analgesic effect of epidural nifedipine (20 μg) a L type calcium channel blocker in male Sprague - Dawley rats. Analgesia was measured by tail flick involving spinal reflexes and by hot plate requiring intact central nervous system. They conclude that nifedipine given epidurally, possesses antinociceptive properties at the dose of 5 micrograms, and higher and it is more prominent at the spinal than the supraspinal level.

Hirota and colleagues studied the effect of lidocaine, bupivacaine on L type voltage activated calcium channels in cerebro cortical membranes prepared from rat brain. They found an interaction between local anaesthetics agents and L types calcium channel.

Sugiyama and Mutelai showed that tetracaine, at concentrations required for spinal anaesthesia, depressed high and low voltage activated calcium channels of dorsal root ganglion cells of rat sensory neurones, the most susceptible being the L-Type Calcium Channel.

A.Fassaulaki, M.Zotou 1998 investigated the effect of IV infusion of mimodepine on the spread of spinal anaesthesia in 50 patients undergoing TURP. His study was associated with a delay in regression of sensory block produced by intrathecal injection of lidocaine.

Calcium channel blockers, including verapamil potentiate the antinociceptive effects of opioids at the spinal cord level. It has also been demonstrated that morphine inhibits calcium ion influx through receptor operated calcium channel in neuronal cells. A proposed mechanism for opioid mediated analgesia at the spinal level is thought to involve reducing presynaptic calcium ion influx, resulting in suppression of neurotransmitters release from primary afferents conveying nociceptive formation. This indicates that antinociceptive effects of intrathecally administered opioids could be increased by intrathecal calcium channel blockers.

Omote K. sonada H., Kawamata M, Namiki 1993 studied the potentiation of antinociceptive effects of morphine by verapamil at the level of spinal cord. They say opioids inhibit voltage dependant calcium conductance which is essential for the nervous system to be able to signal a painful event. Accordingly interference with calcium channel conductance may enhance opioid analgesia. Rats were chronically implanted with lumbar intrathecal catheters. Intrathecally administered drugs were morphine, calcium channel blockers - verapamil, and a combination of morphine and verapamil. Intrathecal morphine showed a significant dose dependant antinociception. In contrast intrathecal verapamil did not show any antinociception. When morphine (5 μgms) and verapamil (50 μgm) were injected together and produced significant antinociception. These interactions were synergistic. The author interpreted these results to indicate that calcium channel blockers synergistically potentiate the analgesic effects of morphine at the level of the spinal cord.

Zarausa R, Tribarren MJ 1991 at University of Nawarra, Department of Anaesthesiology, spain tested the ability of L-type calcium channel blockers and NMDA receptor antagonist magnesium to decrease morphine requirement and pain in post operative period in 92 patients undergoing colorectal surgery. Increase of intracellular calcium plays a key role in spinal transmission of pain and in the establishment of central sensitization. They found no diffierences in post operative morphine consumption by using verapamil or magensium. But in our study the post operative analgesic period is prolonged.

Santillin R, Mastre JM, Hure MA 1994, Department of Anaesthesiology, Santander, spain studied the abiltiy of nimodipine, a L type calcium channel blocker, to enhance morphine analgesia or modify the development of tolerance. They studied in patients with cancer pain who had needed successive increments of morphine for periods ranging from 21 to 780 days. Assessment of daily morphine requirement was the primary effect parameter. Nimodipine suceeded in 16 of 23 patients in reducing daily dose of morphine. these results support the pharmacological interference with Ca^{2+} related events which may modify chronic opioid effects, including expression of tolerance.

Weizman and Getslev 1999 evaluated, the opioid antinociceptive mechanism of Ca^{2+} channel blockers verapamil and flunarizine in groups of mice, with hotplate test. Both produced naloxone sensitive dose dependent analgesia. Both enhanced the antinociceptive activity of morphine implying a role of mu receptors. They also found in their study that the antinociceptive activity of verapamil is also mediated by delta receptor agonistic activity. Verapamil is a partial agonist of Kappa 1 and Kappa 3 receptors. Verapamil's analgesia was explained by agonistic activity at the mu, delta and kappa 3 receptors subtypes. Flunarizine exhibited agonist - antagonistic property. It has agonistic activity at the mu 1 receptor and antagonistic activity at delta, kappa 1 and kappa 3 subtypes.

All these various studies indicates how verapamil produces antinociception. These studies only initiated us to use verapamil epidurally to enhance the duration of analgesia along with bupivacaine.

The altered sensory processing caused by high intense noxious stimuli results in a decrease in thresholds of dorsal horn neurons, an increase in gene expression and increased response of dorsal horn neurons elicited by repititive C-fiber stimulation.

There is activation of excitatory aminoacid receptors followed by release of glutamate and aspartate in the dorsal horns of spinal cord.

These amino acids actions are mediated by NMDA receptors. Activation of neurokinin-1 receptors by substance P produces a slow, prolonged depolarisation and enhances the influx of Ca^{2+} through voltage gated channels. Activation of NMDA receptors leads to Ca^{2+} entry in to the cell through NMDA receptor operated by Ca^{2+} channels and activates phospholipase C. Phospholipase C catalyzes the formation of intracellular second messengers, which causes the release of Ca^{2+} from endoplasmic reticulum.

The increase in intracellular calcium results in increased gene expression and central sensitization including wind up phenomenon and long term potentiation. Thus calcium channel conductance is required for the nervous system to signal a painful situation. A disruption of calcium ion movement interferes with sensory

processing and contributes to antinociception. This principle holds good for the use of verapamil, a L type calcium channel blocker to reduce post operative pain.

This series of reactions may be prevented or attenuated presynaptically by reducing the release of neurotransmitters by using opioids and local anaesthetics or post synaptically by NMDA receptor antagonist like ketamine. There is evidence that ketamine, a clinical NMDA receptor antagonist reduces post operative pain.

Magnesium a physiological calcium channel blocker and NMDA receptor antagonist suppresses NMDA induced adverse behavioural reactions. Nowek *et al.*, 1984 says that extracellular applicaiton of Mg^{2+} reduces calcium current of NMDA receptors. It has been suggested that substances with calcium channel blocking effects and NMDA receptor antagonists may prevent pain and facilitate treatment for established pain states.

Conduction abnormalities were carefully watched during our study with continous ECG monitoring and preoperative as well as post operative 12 lead ECG. Verapamil will slow the conduction around AV node and rarely may produce second or third degree AV block, bradycardia and in extreme cases, asystole. Verapamil causes dose dependent suppression of the SA node and produce brady cardia. But with this 5 mg of verapamil given epidurally we did not experience bradycardia or conduction abnormalities.

There are only limited informations are available on verapamil's effect on pain in humans. In our study we showed that bupivacaine and verapamil administered epidurally produced good analgesic quality and increased the post operative analgesic period in elective herniorraphy surgeries.

V.   Summary

This study assessed the clinical efficacy of Verapamil 5mg added to 0.5% plain bupivacaine in Lumber epidural Anesthesia for elective inguinal surgeries.

The onset time, duration of analgesia, level of sensory blockade, quality of motor blockade, Hemodynamic parameters, Respiratory changes were assessed and the results showed that Verapamil had

- Significant prolongation in the duration of analgesia
- No effect on the time to onset of analgesia
- No effect on the highest level of sensory block
- No significant effect in the degree of motor blockade
- No significant effect on Hemodynamics
- No significant effect on Respiration.

VI.   Conclusion

From this study we conclude that epidural bupivacaine (0.5%) with verapamil prolonged the postoperative analgesic period when compared to 0.5% bupivacaine alone for elective inguinal herniorraphy surgeries under lumbar epidural anaesthesia.

Bibliography

[1].   Aanosen LM, Lei S and Wilcox GL. Excitatory amino acid receptors and nociceptive neurotransmission in rat spinal cord. Pain 1990; 41: 309-321.
[2].   Albillos A, Artalejo AR, Lopez MG, Gandia L, Garcia AG, Carbone E. Calcium channel subtypes in cat chromaffin cells. Journal of Physiol (Lond) 1994; 477: 197-213.
[3].   Anand KJS, Kenneth D. Craig. New perspectives on the definition of pain. Pain 1996; 67: 3-6.
        Annika B. Malmberg and Tony L. Yaksh. Effect of continuous intrathecal infusion of ω-conopeptides, n-type calcium-channel blockers, on behaviour and antinociception in the formalin and hot-plate tests in rats. Pain 1995; 60: 83-90.
[4].   Augustine GJ, Charlton MP and Smith SJ. Calcium action in synaptic transmitter release. Annual Review of Neuroscience 1987; 10-633-693.
[5].   Besson JM and Chaouch A. Peripheral and spinal mechanisms of nociception. Physiology and Review 1987; 67-186.
[6].   Biton B, Granger P, Carreau A. The NMDA receptor antagonist eliprodil (SL 82.0715) blocks voltage-operated Ca^{2+} channels in rat cultured cortical neurons. European Journal of Pharmacology 1994; 218 : 75-81.
[7].   Boll W, Lux HD. Action of organic antagonists on neuronal calcium currents. Neuroscience Letter May 1985; 56: 35-9.
[8].   Brown AM, Sayer RJ, Schwindt PC, Crill WE. P-type calcium channels in rat neocortical neurons. Journal of Physiology (London) 1994; 475: 197-205.
[9].   Chaplan SR, Malmberg AB, Yaksh TL. Efficacy of NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. Journal of Pharmacology Experimental Therapy 1997; 280: 829-838.
        Coderre TJ, Melzack R. The role of NMDA receptor-operated calcium channels in persistent nociception after formalin-induced tissue injury. Journal of Neuroscience 1992; 12: 3671-3675.
[10].   Collingridge GL and Lester RA. Excitatory amino acid receptors in the vertebrate central nervous system. Pharmacology and Review 1989; 41: 143-210.
[11].   Contreras E, Tamayo L, Amigo M. Calcium channel antagonists increase morphine-induced analgesia and antagonize morphine tolerance. European Journal of Pharmacology 1988; 148 : 463-466.
[12].   Damaj MI, Welch SP, Martin BR. Involvement of calcium and L-type channels in nicotine-induced antinociception. Journal of Pharmacology Experimental Therapy 1995; 75: 193-200.
[13].   Dickenson AH. Spinal cord pharmacology of pain. British Journal of Anaesthesia 1995; 75: 193-200.

[14]. Diochot S, Richard S, Baldy-Moulinier M. Dihydropyridines, Phenylalkylamines and benzothiazepines block N-, P/Q- and R-type calcium currents. Arch 1995 Nov; 431: 9-10.
[15]. Do-frul A, Ye filyurt O. Effects of intrathecally administered calcium-channel blockers on acetic acid-induced writhing test in mice. General Pharmacology 1998 Apr; 30: 613-6.
[16]. Dunlap K, Luebke JI, Turner TJ. Exocytotic Ca^{2+} channels in mammalian central neurons. Trends Neuroscience 1995; 18: 89-98.
[17]. Erker T, Laimer I, Huck S. Synthesis and calcium antagonistic activity of KT-362. Archives Pharmacology July 1996; 329: 347-351.
[18]. Fabrio Bordi and Mauro Quartaroli. Modulation of nociceptive transmission by NMDA/glycine site receptor in the ventroposterolateral nucleus of the thalamus. Pain 2000; 84: 213-224.
[19]. Fassoulaki A, Sarantopoulos C, Chondreli S. Systemic fentanyl enhances the spread of spinal analgesia produced by lignocaine. British Journal of Anaesthesia 1991; 67: 437-439.
[20]. Fassoulaki, A, Zotou M. and Sarantopoulus C. Effect of nimodipine on regression of spinal analgesia. British Journal of Anaesthsia 1998; 81: 358-360.
[21]. Filos KS, Goudas LC, Patroni O and Tassoudis Y. Analgesia with epidural nimodipine, Lancet 1993; 342: 1047.
[22]. Fitzgerald M. Development of pain mechanisms. British Medical Bulletin 1991; 47: 667-675.
[23]. Gelbfish JS, Philips T, Rose DM, Wait R. Cunningham JN. Acute spinal cord ischemia: preventation of parapelegia with verapamil. Circulation Sep 1986; 74: 5-10.
[24]. Gilchrist HD, Allard BL, Simone DA. Enhanced withdrawal responses to heat and mechanical stimuli following intraplantar injection of capsaicin in rats. Pain 1996; 67: 179-188.
[25]. Hara K, Saito Y, Kirihara Y, Sakura S, Kosaka Y. Antinociceptive effects of intrathecal L-type calcium channel blockers on visceral and somatic stimuli in the rat. Anesthesia and Analgesia 1998; 87: 382-387.
[26]. Harris RA, Yamanoto H, Loh HH, Way EL. Discrete changes in brain calcium with morphine analgesia, tolerance-dependence and abstinence. Life Science 1977; 20: 501-506.
[27]. Heinricher, MM, McGaraughty S. and Farr DA. The role of excitatory amino acid transmission within the rostral ventromedial medulla in the antinociceptive actions of systemically administered morphine. Pain 1999, 81: 57-65.
[28]. Heinricher M.M and McGaraughty S. Analysis of excitatory amino acid transmission within the rostral ventromedial medulla: implications for circuitry. Pain 1998; 75: 247-255.
[29]. Hess P, Lansmas JB, Tsien RW. Different modes of Ca channel gating behaviour favoured by dihydropyridine Ca agonists and antagonists. Nature 1984; 311: 538-544.
[30]. Hirata S, Enoki T, Kitamura R, Vinh VH, Kakamura and Mori K. Effects of isoflurane on receptor-operated Ca^{2+} channels in rat aortic smooth muscle. British Journal of Anaesthesia, 1998; 81: 578-583.
[31]. Hirota, k, Kudo M, Kudo T, Matsuki A and Lambert DG. Inhibitory effects of intravenous anaesthetic agents on K^{+} - evoked norepinephrine and dopamine release from rat striatal slices: possible involvement of P/Q-type voltage-sensitive Ca^{2+} channels. British Journal of Anaesthesia 2000; 85: 874-80.
[32]. Hirota K, Lambert DG. Voltage-sensitive Ca^{2+} channels and anaesthesia. British Journal of Anaesthesia 1996; 76: 344-6.
[33]. Hirota K, Browne T, Lambert DG. Do local Anaesthetics interact with dihydropyridine binding sites on neuronal L type calcium channels? British Journal of Anaesthesia 1997; 78: 185-188.
[34]. Hoffmeister F, Tettenborn D. Calcium agonists and antagonists of the dihydropyridine type: Antinociceptive effects, interference with opiate μ-receptor agonists and neuropharmacological actions in rodents. Psychopharmacology(Berl) 1986: 90: 299-307.
[35]. Horacio Vanegas, Hans-Georg Schaible. Effects of antagonists to high-threshold calcium channels upon spinal mechanisms of pain, hyperalgesia and allodynia. Pain 2000; 85: 9-18.
[36]. Huhn Choe, Jin-Song Kim, Seong-Hoon Ko, Dong-Chan Kim, Young-Jin Han and He-Sun Song. Epidrual verapamil reduces analgesic consumption after lower abdominal surgery. Anesthesia Analgesia 1998; 86: 786-790.
[37]. Jesen TS and Yaksh TL. The antinociceptive activity of excitatory amino acids in the rat brainstem: an anatomical and pharmacological analysis. Brain Res 1992; 569: 255-267.
[38]. Kapur PA, Flacke WE. Lack of correlation of verapamil plasma level with cumulative protective effects against halothane-epinephrine ventricular arrhythmias. Journal of Cardiovascular Pharmacology 1982; 4: 652-657.
[39]. Kato G, Kelly JS, Krnjevic K, Somjen G. Anaesthetic action of magnesium ions. Canadian Anaesthetic Society Journal 1968; 15: 539-544.
[40]. Keiichi Omote, Hajime Sonoda, Mikito Kawamata, Hiroshi Iwasaki, Akiyoshi Namiki. Potentiation of Antinociceptive effects of morphine by calcium-channel blockers at the level of the spinal cord. Anesthesiology, 1993; 79: 746-752.
[41]. Koining H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra – and postoperation analgesic requirements. Anesthesia and Analgesia 1998; 87: 206-210.
[42]. Kryzhanovski, GI Igon'kina SI. Effects of verapamil on behavioral and microcirculatory disorders in pain syndrome of spinal etiology. Biol Med 1990 May 109; 425-428.
[43]. Lia EN, Prado WA. Effects of intrathecal L and N-type calcium channel blockers on the antinociception evoked by opioid agonists in the rat tail flick test. Acta Physiol Pharmacol Ther Latinoam 1999; 49: 195-203.
[44]. Lux F, Welch SP, Brase DA, Dewey WL. Interaction of morphine with intrathecally administered calcium and calcium antagonists: Evidence for supraspinal endogenous opioid mediation of intrathecal calcium-induced antinociception in mice. Journal of Pharmacology and Experimental Therapy 1988; 246 : 500 – 507.
[45]. Lynch C, Pancrazzio JJ. Snails, spiders and stereospecificity Is there a role for calcium channels in anaesthetic mechanisms? Anaesthesiology 1994; 81: 1-5.
[46]. MacDonald JF, Schneiderman JH. Actions of verapamil on the excitability of cultured neurons. Canadian Journal of Pharmacology Dec 1983; 61:1467-72.
[47]. Malmberg AB, Yaksh TL. Voltage-sensitive calcium channels in spinal nociceptive processing: blockade of N- and P-type channels inhibits formalin – induced nociception. Journal of Neuroscience 1994; 14: 4882-4890.
[48]. Mangiardi IM, Hariman RJ, McAllister RG, Bhargava V, Surawicz B. Shabetai R. Electrophysiologic and hemodynamic effects of verapamil. Correlation with plasma drug concentrations. Circulation 1978; 57: 366-372.

[49]. Mikito Kawamata and Keiichi Omote. Involvement of increased excitatory amino acids and intracellular Ca^{2+} concentration in the spinal dorsal horn in an animal model of neuropathic pain. Pain 1996: 68: 85-96.

[50]. Miljanich GP, Ramachandran J. Antagonists of neuronal calcium channels: structure, function and therapeutic implications. Annual Review of Pharmacology and Toxicology 1995; 35: 707-734.

[51]. Miller SG and Kennedy MB. Regulation of brain type II Ca^{2+}/calmodulin-dependent protein kinase by autophosphorylation: a Ca^{2+} - triggered molecular switch. Cell 1986; 44: 316-332.

[52]. Miranda HF, Bustamante D, Kramer V, Pelissier T, Saavedra H, Paelie C, Fernandez E, Pinardi G. Antinociceptive effects of Ca^{2+} channel blockers. European Journal of Pharmacology 1992; 217: 137-141.

[53]. Nasstrom J, Karlsson U, Post C. Antinociceptive actions of different classess of excitatory amino acid receptor antagonists in mice. European Journal of Pharmacology 1992; 212: 21-29.

[54]. Neugebauer V, Rümenapp P, Schaible H-G. The role of spinal neurokinin-2 receptors in the processing of nociceptive information from the joint and in the generation and maintenance of inflammation – evoked hyper-excitability of dorsal horn neurons in the rat. European Journal of Neuroscience 1996a; 8:249-260.

[55]. Neugebauer V, Lücke T, Schaible H-G, N-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists block the hyperexcitability of dorsal horn neurons during development of acute arthritis in rat's knee joint. Journal of Neurophysiology 1993; 70: 1365-1377.

[56]. Nowycky MC, Fox AP, Tsien RW. Three types of neuronal calcium channel with different calcium agonist sensitivity. Nature 1985; 316: 440-443.

[57]. Omote K, Kitahata LM, Collins JG, Nakatani K, Nakagawa. The antinociceptive role of μ-and δ-opiate receptors and their interactions in the spinal dorsal horn of cats. Anesthesia and Analgesia 1990; 71: 23-28.

[58]. Omote K, Iwasaki H, Kawamata M, Namiki A. Effects of verapamil on spinal anaesthesia with local Anaesthetics. Anaesthesia and Analgesia 1995; 80: 444-448.

[59]. Omote K, Iwasaki H, Ohmori H, Kawamata M, Sumita S, Namiki A. Potentiation of local lignocaine sensory block by calcium channel blockers in rats. British Journal of Anaesthesia 1996; 77: 243-247.

[60]. Patricia A. Kapur, Byron C. Bloor, Werner E. Flacke, Sandra K. Olewine. Comparison of Cardiovascular responses to verapamil during enflurane, isoflurane or halothane anesthesia in the Dog. Anesthesiology, 1984; 61: 156-160.

[61]. Pereira IT, Prado WA, Dos Reis MP. Enhancement of epidural morphine induced analgesia by systemic nifedipine. Pain 1993; 53: 355-357.

[62]. Pozo ED, Caro G, Baeyens JM. Analgesic effects of several calcium channel blockers in mice. European Journal of Pharmacology 1987; 137: 155-160.

[63]. Rosa Ssantillan, Maria A. Hurle, Juan A. Armijo, Rosario de los Mozos, Jesus Florez. Nimodipine-enchanced opiate analgesia in cancer patients requiring morphine dose escalation: a double-blind, placebo-controlled study. Pain 1998; 76: 17-26.

[64]. Sluka KA. Blockade of calcium channels can prevent the onset of secondary hyperalgesia and allodynia induced by intradermal injection of capsaicin in rats. Pain 1997; 71: 157-164.

[65]. Sluka KA, Westlund KN. An experimental arthritis in rats: dorsal horn aspartate and glutamate increases. Neuroscience Letter 1992; 145: 141-144.

[66]. Sluka KA. Blockade of N and P/Q-type calcium channels reduces the secondary heat hyperlgesia induced by acute inflammation. Journal of Pharmacology Experimental Therapy 1998; 287L 232-7.

[67]. Tao PL, Lee CR, Law Py, Loh HH. The interaction of the mu-opioid receptor and G protein is altered after chronic morphine treatment in rats. Naunyn-Schmiedebergs Arch Pharmacol 1993; 348: 504-508.

[68]. Tram MR, Schneider J, Marti R, Rifat K. Role of magnesium sulphate in postoperative analgesia. Anesthesiology 1996; 84: 340-7.

[69]. Tsien RW, Lipscombe D, Madison DV, Bley KR, Fox AP. Multiple types of neuronal calcium channels and their selective modulation. Trends in Neuroscience 1988; 11: 431-438.

[70]. Tsuchida H, Seki S, Tanaka S, Okazaki K and Namiki A. Halothane attenuates the endothelial Ca^{2+} increase and vasorelaxation of vascular smooth muscle in the rat aorta. British Journal of Anaesthesia 2000; 84: 215-20.

[71]. Wall PD. The prevention of post-operative pain . Pain 1998; 33: 289-90.

[72]. Wang YX, Pettus, Luther RR and Bowersox SS. Effects of the selective. N-type calcium channel blocker, SNX-111, on the development of tolerance to spinal morphine analgesia in rats. Neuroscience Abstract 1997; 23: 1121.

[73]. Wang Y-X, Pettus M, Philips C, Gao D, Bowersox SS, Luther RR. Antinociceptive properties of a selective neuronal N-type calcium channel blocker, ziconotide (SNX-111), in a model of post-operative pain. Society of Neuroscience Abstract 1998; 24: 1626.

[74]. Wang YX, Pettus M, Luther RR, Bowersox SS. Effects of the selective N-type calcium channel blocker, ziconotide, on the development of tolerance to spinal morphine analgesia in rats. Neuroscience Society Abstract, 1997; 23: 1121.

[75]. Wang YX, Pettus M, Philips C, Gao D, Bowersox SS and Luther RR. Antiniciceptive properties of a selective, neuronal N-type calcium channel blocker, Zinconotide (SNX-111), in a rat model of post-operative pain. Neuroscience Abstract 1998; 24: 1626.

[76]. Wei Zy, Karim F, Roerig SC. Spinal morphine/clonidine antinociceptive synergism: involvement of G proteins and N-type voltage-dependent calcium channels. Journal of Pharmacology Experimental Therapy 1996; 278: 1392-1407.

[77]. Weizmen R, Getslev V, Pankova IA, Pick CG. Pharmacological interaction of the calcium channel blockers verapamil and flunarizine with the opioid system. Brain Res Feb 1999; 818: 817-195.

[78]. Welch SP, Stevens DL, Dewey WL. A proposed mechanism of action for the antinociceptive effect of intrathecally administered calcium in the mouse. Journal of Pharmacology Experimental Therapy 1992; 260: 117-127.

[79]. Yaksh TL. Spinal opiate analgesia: characterstics and principles of action. Pain, 1981; 11: 293-346.

[80]. Yaksh TL. In vivo studies on spinal opiate receptor system mediating antinociception: I. Mu and delta receptor profiles in the primate. Journal of Pharmacology Experimental Therapy 1983; 226: 303-316.

[81]. Yong CH, Dey P, Yarmusch J, et al., Nifedipine induced analgesia after epidural injection in rats. Anaesthesia and Analgesia1994; 79: 303-6.

[82]. Yoshito Takano, Eiru Sato, Toshihiko Kaneko and Isao Sato, Antihyperalgesic effects of intrathecally administered magnesium sulfate in rats. Pain 2000; 84: 175-179.

[83]. LI, Fleisher LA, Wiener-Kronish JP, Young WL, eds. Miller's Anasthesia. 7th ed. Philadelpia: Churchill Livingstone Inc, 2009: 913-940.

[84].   Smith FL, LeBlanc SJ, Carter R. Influence of intracellular Ca2+ release modulating drugs on bupivacaine infiltration anesthesia in mice. Eur J Pain 2004;8(2):153-161.

[85].   Karakaya D, Baris S, Ozkan F, Demircan S, Gok U, Ustun E, Tur A. Analgesic effects of interpleural bupivacaine with fentanyl for postthoracotomy pain. J Cardiothorac Vasc Anesth 2004;18(4):461-465.

[86].   Pirec V, Charles E, Laurito MD. The combined effect of N type calcium channel blockers and morphine on A delta versus C fibre mediated nociception. Anesth Analg 2001;92:239-243.

[87].   Kim WM, Yoon MH, Cui JH. Role of PKG-L-type calcium channels in the antinociceptive effect of intrathecal sildenafil. J Vet Sci 2010;11(2):103-106.

[88].   Scott NB, Absalom AR. The features of regional anaesthesia. In: Wildsmith JAW, Armitage EN, McClure JH, eds. Principles and practice of regional anaesthesia. 3rd ed. New York: Churchill Livingstone Inc, 2003: 9–20.