Comparison Of Efficacy Of Oral Pregabalin And Oral Paracetamol As Pre-Emptive Analgesics In Patients Receiving Spinal Anesthesia For Lower Limb Surgeries.

by

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Dissertation submitted to

In partial fulfillment for the degree of

DOCTOR OF MEDICINE
IN
ANAESTHESIA

Under the Guidance of

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2020

ABBREVIATION

ASA	-	American society of Anesthesiology
COX	-	Cyclooxygenase
DBP	-	Diastolic blood pressure
GABA	-	Gamma amino butyric acid
GAD	-	Glutamic acid decarboxylase
ECG	-	Electrocardiogram
HR	-	Heart rate
MD	-	Mean deviation
Std	-	Standard deviation
SBP	-	Systolic blood pressure
VAS	-	Visual analogue score
PONV	-	Postoperative nausea and vomiting
NSAIDS	-	Non steroidal anti-inflammatory drugs
CSF	-	Cerebrospinal Fluid
i.v.	-	Intravenous
ml	-	millilitre
HRS	-	Hours

ABSTRACT

BACK GROUND & AIM

After any surgery patients continue to experience unacceptably high levels of pain post operatively, this is generated through multiple mechanisms. Effective management of postoperative pain leads to increased patient satisfaction; earlier mobilization and reduced hospital stay. One of the methods used for management of postoperative pain is pre-emptive analgesia -blockade of afferent nerve fiber before surgical stimulus.

Based on the multimodal post-operative pain management concept, recent studies shows that use of pre-emptive Paracetamol or Pregabalin are an effective adjuvant in treatment of post-operative pain and decreases the post-operative opioid use.

Aim of this study was to evaluate the efficacy of preemptive Pregabalin and Paracetamol and comparison between the two.

MATERIALS AND METHODS

The study was a prospective randomized comparative study, conducted at ——— on 120 patients posted under spinal anaesthesia for lower limb surgeries from December 2017 to August 2019.

a) **Inclusion criteria:**

1. Patients from age 20-65yrs undergoing elective surgery.
2. ASA grade I and II.

b) Exclusión criteria :

1. Uncooperative and unwilling patient.
2. Hypersensitivity to drugs.
3. History of neurologic or seizure disorder.

4. Surgeries lasting for more than 3 hours

The study population of 120 patients of ASA grade I and ASA grade II with age and sex matched were randomly selected and divided by computer generated random number tables in to two groups with 60 patients in each group. The study was initiated after obtaining clearance from ethical committee. Written informed consent was obtained from all the patients included in the study. Patients were explained about visual analogue score.

GROUP PG- Received Pregabalin 150 mg orally 1 hour prior to surgery with 5ml of water.

GROUP PA- Received Paracetamol 1gm orally 1 hour prior to surgery with 5ml of water.

Spinal anaesthesia technique was standardized to all patients. Post operative pain was assessed with using visual analogue score at 2, 4, 6, 12, 24 hours after surgery.

RESCUE ANALGESIA.

If visual analogue score more than 3, rescue analgesia was given in the form of Inj. Tramadol 1mg/kg. Time of first rescue analgesic and total amount of analgesic given over 24 hours was noted.

RESULTS

In our study mean age distribution in group PG was 41.70±13.96 and in group PA 40.23±12.62. The age distribution was higher in group PG compared to group PA . The two groups were comparable on the basis of gender and ASA grade. Group PG has significantly less VAS score then group PA for 24 hours of Post operative period. The mean visual analog score for group PG at 2, 4, 6, 12, and 24 hours after surgery was lower as compared to the corresponding rates for the group PA. This difference in VAS scores was significant for all times except at time 4 hrs and 6 hrs after surgery ($p<0.05$).The time of first rescue analgesia

(4.3±1.2 hrs Group PG vs. 3.3±1.1 Hrs Group PA) and total number of rescue analgesia in the 24 hours period post operatively in the form of tramadol 1mg/kg was significantly lesser for group PG compared to group PA (1.6±0.6 Group PG vs. 2.9±0.7 Group PA). We confronted nausea and vomiting in 9 cases of which, 6 were in group PG and 3 were in group PA. No other significant side effects were noted.

CONCLUSIONS

Based on the findings of the study, we can conclude that pre-operative administration of oral Pregabalin 150mg was an effective and a safe adjuvant for acute pain after surgery compared to oral Paracetamol 1000 mg. Pregabalin reduces the postoperative pain score and total analgesic consumption and there were no other significant side effects in the postoperative period.

Key WORDS:

Pre-emptive Analgesia, Pregabalin, Paracetamol, Postoperative Pain, Visual Analogue Score, Tramadol, Rescue Analgesia

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INTRODUCTION

Postoperative pain remains a challenging problem and many patients undergoing surgery continue to experience unacceptably high levels of pain post operatively, which is generated through multiple mechanisms.[1]

Effective management of postoperative pain leads to increased patient satisfaction; earlier mobilization and reduced hospital stay. One of the methods used for management of postoperative pain is pre-emptive analgesia - blockade of afferent nerve fiber before surgical stimulus. "Pain signals from damaged tissue are not transmitted to the central nervous system (CNS) through hard-wired pathways. In contrast, nociceptive signals once initiated, will launch a cascade of alterations in the somatosensory system, including an increase in the responsiveness of both peripheral and central neurons. These alterations will increase the response to subsequent stimuli and thus amplify pain".[2]

Pre-emptive analgesia reduces the physiological consequences of nociceptive transmission provoked by the procedure. Owing to this protective effect on the nociceptive pathways, pre-emptive analgesia has the potential to be more effective than a similar analgesic treatment initiated after surgery. Consequently, immediate postoperative pain may be reduced and the development of chronic pain may be prevented. It modifies the peripheral and central nervous system processing of noxious stimuli, reduces post- operative pain and opoid consumption.[3]

Based on the multimodal post-operative pain management concept, recent studies shows that pre-emptive use of NSAIDS, Paracetamol or Pregabalin are an effective adjuvant in treatment of post-operative pain and decreases the post-operative opioid use.[4]

Pregabalin is a structural analogue of gamma amino butyric acid (GABA). It

acts by presynaptic binding to alpha-2-delta subunit of voltage gated calcium channels that are widely distributed in spinal cord and brain. By this mechanism, Pregabalin modulates the release of several excitatory neurotransmitters, such as glutamate, nor epinephrine, substance-P and Calcitonin gene related peptide. It leads to inhibitory modulation of overexcited neurons and returns them to a normal state. Centrally, Pregabalin could reduce the hyper excitability of the dorsal horn neurons that is induced by tissue damage. Based on these properties Pregabalin was used as pre-emptive analgesia. [5,6]

Paracetamol inhibits both isoform of cyclooxygenase COX-1 and COX-2. Current evidence points to multisite activity in the central nervous system involving inhibition of prostaglandin synthesis and interaction with both serotonergic and cannabinoids pathways. Paracetamol has been used successfully in management of postoperative pain when used pre-emptively and this has been demonstrated by several studies.[7]

Literature search revealed that are very few studies that compare Pregabalin and Paracetamol as pre-emptive analgesic. With this background we planned to study and compare the analgesic effect of both the drugs as pre-emptive analgesic.

AIMS AND OBJECTIVES

1. Assessing the analgesic efficacy of pre-emptive Pregabalin in terms of duration and quality.
2. Assessing the analgesic efficacy of pre-emptive Paracetamol in terms of duration and quality.
3. To Compare post -operative analgesia of both Drugs.
4. Adverse effect of either drug.

REVIEW OF LITERATURE

Ibrahim M *et al.*, (2008) did a Comparative study between Paracetamol and two different doses of preoperative administration of Pregabalin (150 or 300 mg). The use of 150mg of Pregabalin was found to be an effective and a safe adjuvant for acute pain after surgery. They concluded that single preoperative dose administration of Pregabalin (150 or 300mg) had a significant opioid sparing effect in first 2 hours after surgery compared to Paracetamol.[8]

Joon HO Kim *et al.*, (2010) conducted a study to assess the "efficacy of preemptive analgesia with Pregabalin in Septoplasty surgeries. Observed that Visual analog scores for pain were lower in the Pregabalin group than in the placebo group. The number of patients who needed rescue analgesics was lower in the Pregabalin group. The incidence of nausea and vomiting did not differ between groups, and the incidence of sedation was higher in the placebo group. Hence they concluded that perioperative administration of oral Pregabalin 150 mg is an effective and safe way to reduce early postoperative pain in patients undergoing septoplasty".[9]

A. Agarwal *et al.*, (2011) did a randomized placebo controlled double blind study to evaluate the efficacy of single preoperative dose of oral Pregabalin for attenuating postoperative pain and fentanyl consumption after laparoscopic cholecystectomy under general anesthesia. Authors noted that postoperative pain and postoperative fentanyl consumption were reduced in the Pregabalin group compared to the placebo group. Hence they concluded that single dose of preoperative oral Pregabalin of 150mg is an effective method for postoperative pain relief in patients undergoing laparoscopic cholecystectomy under general anesthesia.[10]

Mohamed Ommiad *et al.*, (2012) evaluated the pre-emptive analgesic properties of Pregabalin. "Study was performed on 40 patients who underwent lower

abdominal surgeries. Group I received 300 mg Pregabalin and Group II was given a placebo in oral capsule form. They observed that a 300 mg Pregabalin administered pre-operatively is an efficient and safe agent for pre-emptive analgesia. Premedication with Pregabalin reduces postoperative pain scores and total analgesic consumption without increasing sedation or other side effects in the postoperative period".[11]

Prashanth Gowtham Raj SK *et al.*, (2012) conducted a study to assess the "efficacy of Preemptive oral Pregabalin for prolonging post-operative analgesia in modified radical mastectomies. The postoperative VAS scores were significantly lower and duration of analgesia was longer in Pregabalin group as to control group. The total analgesic consumption, PONV scores were also lower in Pregabalin group. Ramsay sedation scores were slightly higher in Pregabalin group but were acceptable clinically. The side effects were similar in both groups. They concluded that, Preemptive 150mg oral Pregabalin reduces post- operative pain scores (VAS) significantly, provides longer duration and better quality of post- operative analgesia, reduces opioid analgesic requirement and attenuates hemodynamic response to laryngoscopy, endotracheal intubation and also extubation without increase in the side effects when used in optimal doses".[12]

Anita Kumari *et al.*, (2013) studied the "effect of oral Pregabalin with placebo as premedicant on post-operative analgesia in patients undergoing hysterectomy after spinal anaesthesia. They observed that the mean duration of effective analgesia was comparable in both Pregabalin and placebo group. The mean VAS scores in Pregabalin group were significantly reduced compared to the placebo group. The mean number of doses of rescue analgesia in the first 24 hours were significantly less in Pregabalin group compared to Paracetamol group. There were no

significant hemodynamic changes in both groups. Incidence of perioperative adverse effects was similar in both. Hence they concluded that Pregabalin 75mg as premedication increases the duration of spinal analgesia and VAS score. Number of doses of rescue analgesics used was significantly less in the Pregabalin group compared to the placebo group".[13]

Hamid Reza Amiri *et al.,* (2013) conducted a "Multi-Modal Pre-emptive Analgesia with Pregabalin, Acetaminophen, Naproxen, and Dextromethorphan in Radical Neck Dissection surgery. They observed that Postoperative pain was significantly lower for the study group than the control group. Total morphine doses for the pre-emptive analgesia group were 45% lower than those of the other group. Side effects were similar for both groups. They concluded that, single preoperative oral dose of Pregabalin, Acetaminophen, dextromethorphan, and naproxen one hour before surgery is an effective method for reducing postoperative pain and morphine consumption in patients undergoing radical neck dissection".[14]

Gholamreza Khalili *et al.,* (2013) evaluated the "effect of pre-emptive Acetaminophen with control group on postoperative pain score. They observed that Pain scores were lower in pre- emptive Acetaminophen groups at 6 hours after surgery than in the placebo group. There were no differences in pain scores after 6 hours between the pre-emptive a groups. Total analgesic consumption 24 hours after surgery was lowest in the pre-emptive Acetaminophen group. Average time to initial analgesic requirement was slightly longer in the pre-emptive Acetaminophen groups than the control group. Hence they concluded that Pre-emptive Acetaminophen may enhance analgesia and decrease postoperative analgesic consumption".[15]

A. **Sreenivasulu *et al.,* (2014**) determined the" effect of pre-emptive use of 1g intravenous (IV) Paracetamol on post-operative pain scores and analgesic

requirements in patients undergoing laparoscopic surgeries under general anaesthesia. They observed that, at 15 min and 30 min, mean pain scores of normal saline group were significantly more than those of Paracetamol. At 1, 2, and 6 h, mean pain scores of the two groups were comparable and statistically not significant. The requirement of tramadol as rescue analgesia in group normal saline was significantly more than group Paracetamol. The incidence of PONV in the group normal saline was more than group Paracetamol. From their study they concluded that Pre- emptive administration of 1 g of IV Paracetamol in patients undergoing laparoscopic surgeries provided satisfactory analgesia and decreased post-operative tramadol consumption".[16]

Bhawana Rastogi *et al.*, (2015) studied the Postoperative analgesia after laparoscopic Cholecystectomy by pre-emptive use of intravenous Paracetamol or ketorolac. Post - operative VAS scores were persistently higher in Paracetamol group with statistically significant difference. All 45 patients in Paracetamol group and 8 patients in ketorolac group required rescue analgesic within 6 hours of study time. Total tramadol consumption was much higher (2250 mg) in Paracetamol group as compared to 400 mg in ketorolac group they concluded that Pre-emptive use of ketorolac exerted superior Post-operative analgesia after laparoscopic cholecystectomy in comparison to Paracetamol without any significant side effect.[17]

Bon Sebastian *et al.*, (2016) evaluated the "effect of Oral Pregabalin as Pre-emptive Analgesic in Patients Undergoing Lower Limb Orthopaedic Surgeries under Spinal Anaesthesia. They observed that Time for rescue analgesia was significantly increased in Group Pregabalin than in Group control. The total dose of diclofenac required in the 24 hour postoperative period was significantly lower in Group Pregabalin than in Group control. The sedation scores and patient satisfaction scores

were also more in Group Pregabalin than in Group control. They concluded that Pre-emptive Pregabalin in an oral dose of 150 mg offers good postoperative analgesia in lower limb orthopaedic surgeries under spinal anaesthesia".[18]

Tashi Chotton *et al.,* (2015) conducted a study on 90 patients, to assess the effect of pregabalin for relief of postoperative pain after abdominal hysterectomy. They noted the result both static (at rest) and dynamic (during coughing) pain score (VAS) and the consumption of rescue analgesia (ketorolac) were significantly (<0.001) less in the Pregabalin group. There were no significant differences in the postoperative nausea and vomiting, and Ramsay sedation scale. Hence from their studied that concluded that Preoperative Pregabalin had significant effect in relieving postoperative pain when given as an adjuvant.[19]

Nepal Chandra Saha *et al.,* (2015) did a "comparative study on Pre-emptive oral Paracetamol in laparoscopic cholecystectomy surgery. Observed that the total amount of Pethidine needed was significantly lower in the case Paracetamol group the control group. The pain scores were comparatively low in study group than that in the control group from beginning to endpoint of evaluation following the operation. The complaint of nausea at 6 and 12 hours was much less in the case group than that in the control group. Majority (80%) of patients in control group demanded analgesic (pethidine) 10 minutes earlier after operation as opposed to only 8% of the control group .They concluded that Pre-emptive Paracetamol reduces the intensity of postoperative pain and requirements of Pethidine to a large extent with no significant side effects".[20]

SSUnal *et al.,* (2015) studied the effect of intravenous pre-emptive Paracetamol on postoperative fentanyl consumption in patients undergoing open nephrectomy. They concluded that in patients undergoing open nephrectomy, use of

pre-emptive or postoperative paracetamol reduces fentanyl related nausea/vomiting without a decrease in total fentanyl consumption in the early postoperative period. Furthermore, use of pre-emptive or postoperative paracetamol reduces total fentanyl requirements in the first 24 h postoperatively providing a safe and effective postoperative analgesia.[21]

Jokela R *et al.*, (2016) did a study on 90 patients undergoing day-case gynecological laparoscopic surgery received Pregabalin 75 mg or 150 mg or diazepam 5 mg as placebo. All patients received post-operative ibuprofen 800mg twice a day, and a combination of Acetaminophen and codeine as rescue analgesic. Results showed better post-operative analgesia in 150 mg Pregabalin group but no reduction in total amount of post-operative analgesics required. Hence they concluded that single dose of preoperative oral Pregabalin of 150mg is an effective method for postoperative pain relief in patients undergoing laparoscopic cholecystectomy under general anesthesia.[22]

Chetna Jadeja *et al.*, (2016) did a Comparative study on 60 ASA1 and ASA2 patient using a single dose of pre- emptive Pregabalin vs. placebo for post –operative pain relief in middle ear surgery. In this study, it was demonstrated that pre-emptive oral Pregabalin reduces Diclofenac requirement post-operatively. Only side effect that was statistically significant was sedation which was higher in Pregabalin group as compared to placebo group. So it was concluded that single dose preoperative Pregabalin improves analgesia in early postoperative period and reduces analgesic consumption but with increased sedation without respiratory depression.[23]

M Bindu *et al.*, (2016) did a "comparative study with Pregabalin and placebo group on 60 patients. They concluded that Single oral dose of Pregabalin was effective in reducing acute postoperative pain in thyroidectomy patients. It prolongs

the time to the request of rescue analgesia and also results in lower postoperative pain scores in the immediate postoperative period. However a statistically significant low opioid consumption could not be proved".[24]

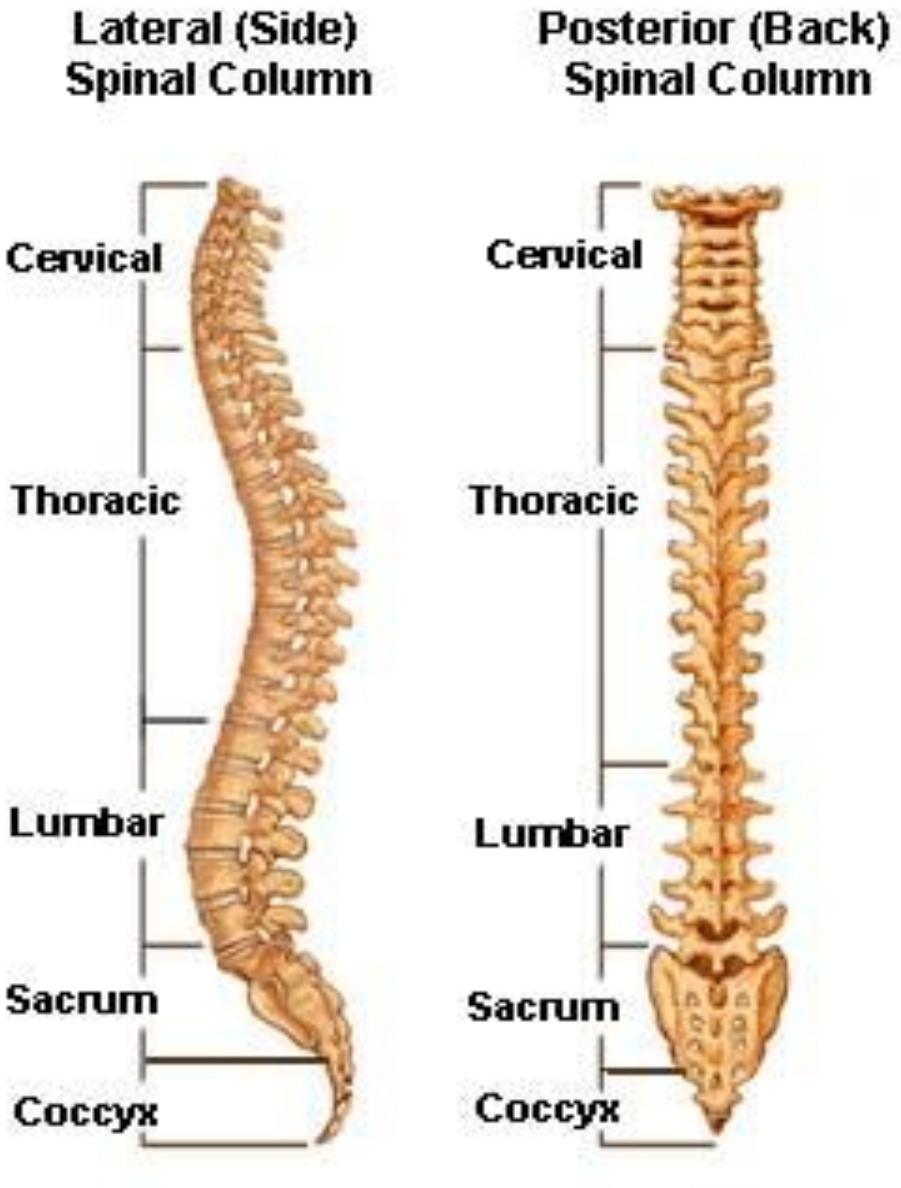
Mustafa Arslan *et al.*, (2016) conducted a study to determine the post-operative analgesic effects of pre-emptive intravenous Paracetamol and the amount of reduction in tramadol consumption and concluded that pre-emptive iv Paracetamol provided effective and reliable pain control after cholecystectomy surgeries and reduced post-operative pain scores, the need for and use of supplementary opioids and the time to first request of analgesics.[25]

BASIC SCIENCE

ANATOMY OF SPINAL CORD[26-28]

For anaesthesiologists, comprehensive understanding of the vertebral column anatomy and Especially that of the lumbar vertebra is crucial.

The mean spinal cord length for males is 45 cm and 42 cm for women. The mean weight is around 30 g.



There are 33 vertebrae in the spinal column: [26, 27]

7(seven)	Cervical vertebrae
12(twelve)	Thoracic vertebrae
5(five)	Lumbar vertebrae
5(five fused)	Sacrum vertebrae
4(four fused)	Coccyx vertebrae

The curves of the spine:

In adult, the normal vertebral column has 4 curves,

1. Cervical spine curve -- convexity anterior
2. Thoracic spine curve -- convexity anterior
3. Lumbar spine curve -- convexity posterior
4. Sacrococcygeal curve — convexity posterior

The curves of the spine are of additional importance when the patient is either in supine or horizontal position.

The 3rd lumbar vertebrae (L3) is the highest point of the spinal curve and the 5th thoracic vertebrae (T5) is the lowest point.

The typical vertebrae:

It is composed of,

1. Anteriorly, the body that bears and transfers the weight and is separated by intervertebral disc from adjacent vertebral bodies.
2. The vertebral archadhered to the body, consisting of two pedicles anteriorly a nd two lamina posteriorly, surrounding and protecting the spinal cord.
3. The transverse processes are at the junction of pedicles and laminae, and the spinous process is where the laminae meet. There are 2 transverse processes a nd 1 spinous process to those ligaments and muscles are attached.
4. Articular processes are four in number - superior 2 and inferior 2.

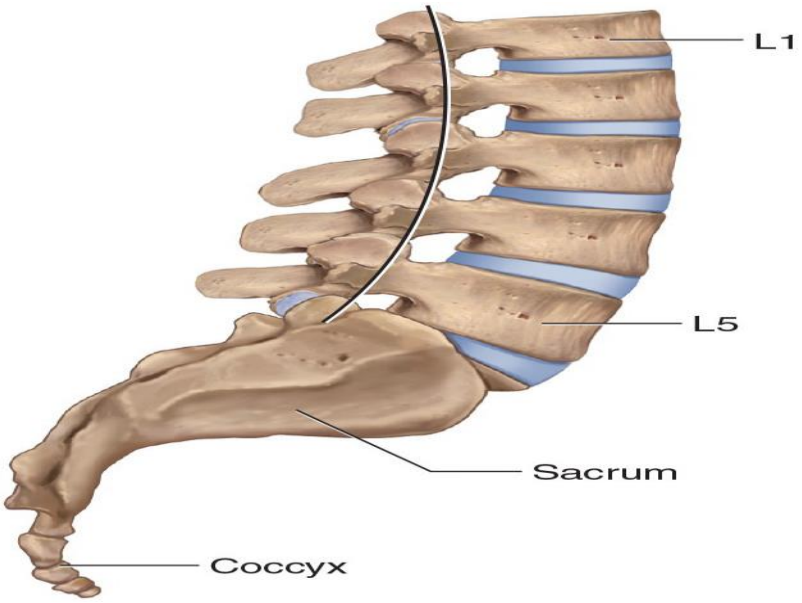
The Lumbar Vertebrae[28]:

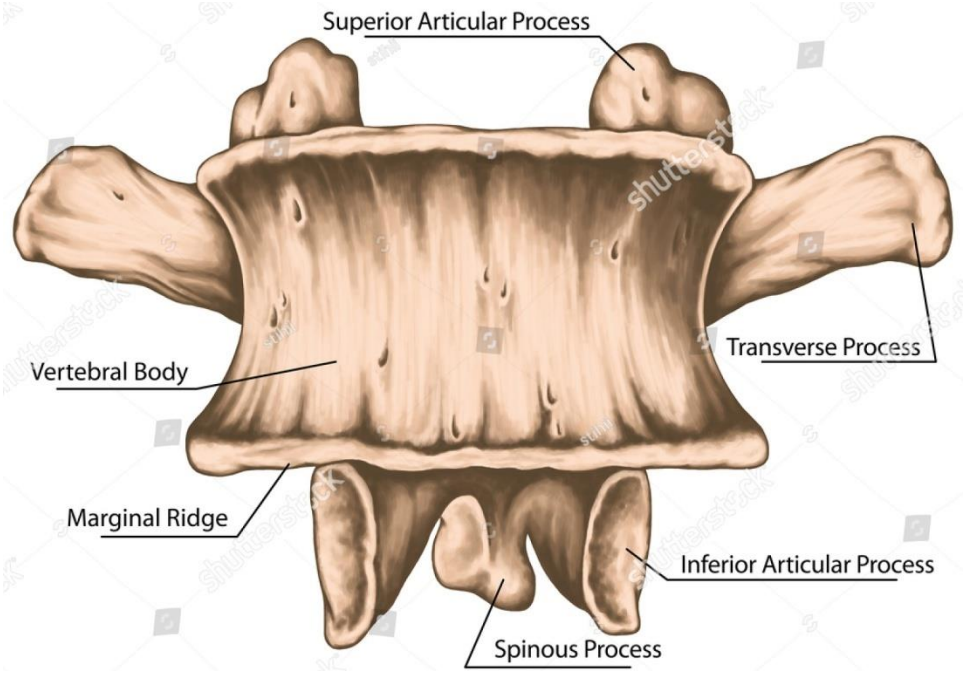
The lumbar vertebrae differ from other vertebrae:

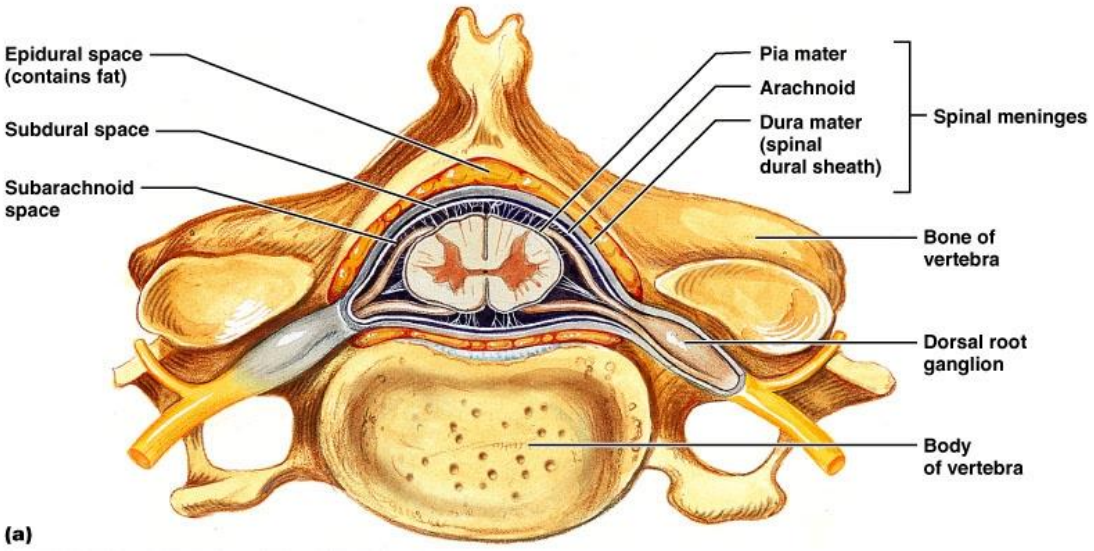
- Lumbar vertebrae bodies are large and kidney shaped.
- The vertebral foraminae are triangular & intermediate in size between those in the cervical and thoracic region.
- The pedicles are thick and short.
- Transverse processes increase slightly in length from L 1 to L 3 and then shorten aga in.
- The laminae are short and along its posterior and inferior borders, the lumbar spinous process is almost horizontal, quadrangular and thickened & oblong to not overlap each other.
- The fifth vertebra produces the lumbosacral angle. Its transverse processes although short & thick are strong and arise not only from the arch but also from the side of the vertebral body.

Intervertebral discs:

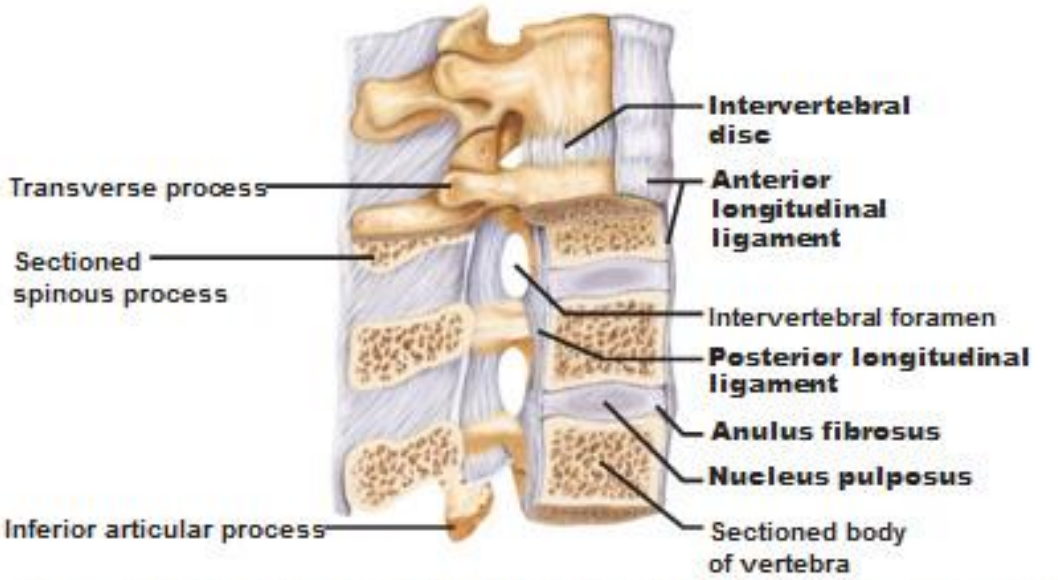
The intervertebral discs account for about onefifth of the vertebral column len gth composed of the outer Fibrous cover, the annulus fibrosus enclosing the nucleus pulposus, a core of smooth gelatinous material. The intervertebral disc gives flexibility to the spinal column and acts as shock absorber. Osteoporosis of the vertebra in addition to atrophy of the intervertebral discs leads to kyphotic old age deformation and reduced height.


L1
L5
Sacrum
Coccyx


Superior Articular Process
Transverse Process
Vertebral Body
Marginal Ridge
Inferior Articular Process
Spinous Process



Ligaments of the Spine



(a) **Median section of three vertebrae, illustrating the composition of the discs and the ligaments**

The Vertebral Ligaments:

For practicing spinal anesthesia, it is essential for an anesthesiologist to have appropriate knowledge of the ligaments of the spinal column by which the spinal nee dle passes.

The distinct sensations of resistance that these ligaments produce to the advancing needle can be felt with experience by the operator.

- **Supra-spinous ligament:** Is a continuation of ligamentum nuchae, strong thick dense fibrous cord that connects the apices of spines from the sevength c ervical vertebrae to the sacrum. This can get ossified in old age and make diffi cult to penetrate with a spinal needle.
- **Inter-spinous ligament:**

  It joins spinous processes adjacent to it. Subsequently they fuse posteriorly with the Supraspinous ligaments and anteriorly with ligamentum flavum.
- **Ligamentum flavum:** It extends from the inner surface and lower border of one lamina to the outer surface and upper border of the lamina below. It is made up of elastic yellow fibers.It includes over half of the vertebral canal's post erior wall, the remaining bony laminae. In the cervical region, ligamentum flavum is the thinest and the thickest in the lumbar region.Functionally, these ligaments are m uscle spares that help to recover from effect of posture after bending and maintain an erect posture.
- **Anterior longitudinal ligament:** It runs along the anterior surface of vertebral bodies from C2 to sacrum.
- **Posterior longitudinal ligament** :

  It stretches along the posterior surfaces of the vertebral bodies from which the basivertebral veins separate it.

Vertebral Canal:

It extends from the foramen magnum to the sacrum's tip. Anteriorly bounded b y the vertebral bodies and intervertebral discs.The laminae, the ligamentum flavum, a nd the vertebral arch posteriorly.

Vertebral canal Contents

- Meninges which enclosed the spinal cord and CSF.
- Spinal nerve roots.
- Fat, vessels and areolar tissue of the extradural space.

Spinal cord[29-31]:

It is an elongated part of the central nervous system that occupies upper two thirds of the vertebral canal, span of 42-45 cms in length, and weighs about 30 gms. It extends from the upper border of the atlas vertebra to that of the lower border of 1st lumbar vertebra or upper border of the 2^{nd} lumbar vertebra above it, the medulla oblongata continues and below it tapers into a conical conus medullaris. A delicate fibrous filament descends from apex of conus medullaris to back of first segment of coccyx is known as the filum terminale. The cord has two enlargements cervical and lumbar corresponding to the nerve supply of the upper and lower limbs. The cervical enlargement extends from C3 to L2 and lumbar enlargement from T9 to T12.

At birth, the tip of spinal cord end at the level of lower border of L3 vertebra and In the adult, it ends at L1-L2 vertebra.

The meninges:

Three membranes enclose the spinal cord from the outside to the inside

1) **Duramater:**

Is a circular sac or sleeve that surrounds the spinal cord. It consists of the Inner (meningeal) layer which is the cranial duramater continuation and the outer

(endosteal) layer which is the vertebral canal periosteum lining, and is separated from the spinal dura by the extradural space. Above, it is tightly attached to the circumference of the foramen magnum. Below it usually streches to the lesser border of S2 vertebra, and then continues as the coating of filum terminale to end by attaching to the periosteum on back of the coccyx. Main fibres of the duramater are longitudinal; lumbar puncture needle should be inserted with its bevel separating rather than cutting these fibres.

2) **Arachnoid mater:**

It is a delicate non-vascular membrane that is closely applied to the dura mater. It is separated from the duramater by subdural space and from piamater by subarachnoid space. Above it continues with cerebral arachnoid, below it widens out, invests the cauda equina and ends at the lower border of S2 vertebra.

3) **Pia mater:**

It is the innermost membrane is a vascular sheath which closely invests the brain & spinal cord and sends delicate septa into its substance. The spinal pia is thickened anteriorly into the lineasplendens along the length of anterior median fissure, on either side it forms ligamentum denticulatum which projects into subarachnoid space and is attached by series of pointed processes to the dura as far down as the first lumbar nerve.

Subarachnoid space:

The subarachnoid space is the space between the arachnoid and pia mater. This space is traversed by cobweb trabeculae and by the cranial & spinal nerves. The spinal fluid bathes these. The space is annular in the cranial and thoracic and is about 3mm deep. Below the 1st lumbar it is circular. The space communicates with the tissues spaces around the vessels in the piamater which accompany them as they penetrate into cord. These continuations have been described as the breaking up into fine ramifications, which surround individual nerve cells (Virchow robin space) and this has been considered as pathway by which a spinal anesthetic solution permeates cord.

Spinal segments:

The pair of spinal nerves which emerge from it divide the cord into segments. These pairs are 31 in number and are: Cervical--08, Thoracic--12, Lumbar 05, Sacral --05, and Coccygeal -- 01.

There are no epineural sheaths in the nerve roots within the dura and are theref ore easily affected by the doses of analgesic drugs brought into contact with them.

Spinal nerves:

"Anterior root & posterior root these 2 fuse together making spinal nerves. Efferent and motor is the anterior root.Sympathetic preganglionic axons emerge from T1 to L2 cells in the spinal cord's intermediolateral horn.

Blocking these fibers affects some of the endocrine gland's reaction to surgical stress. The posterior root is larger than anterior and afferent impulses from whole body including the viscera passes through these roots. Each posterior root has a ganglion and carries fibers of pain, touch, temperature, deep sensation from bone joints and muscles and tendons / efferent from viscera (acco

mpanying sympathetic) and vasodilator fibers. Pain and temperature fibers enter the p osterior horn and end around the cell in gray mater, then cross to the contralateral side of the within three segments and rise in the lateral spinot.

In the posteriorcolumn and spinocerebellar tracts, deep or muscle sensory imp ulses ascend. In the posterior column, the vibration impulses ascend''[29-31].

Sensitivity of different fibres:

Local anesthesia affects all nerve fibres,but within any one fiber type, there is a tendency for smaller,slower conducting fibers to be more easily blocked than large, fast conducting fibres. Myelinated preganglionic B fibres which have a faster conduction time are about three times more sensitive to local anesthetics than the slower non myelinated postganglionic C fibres.

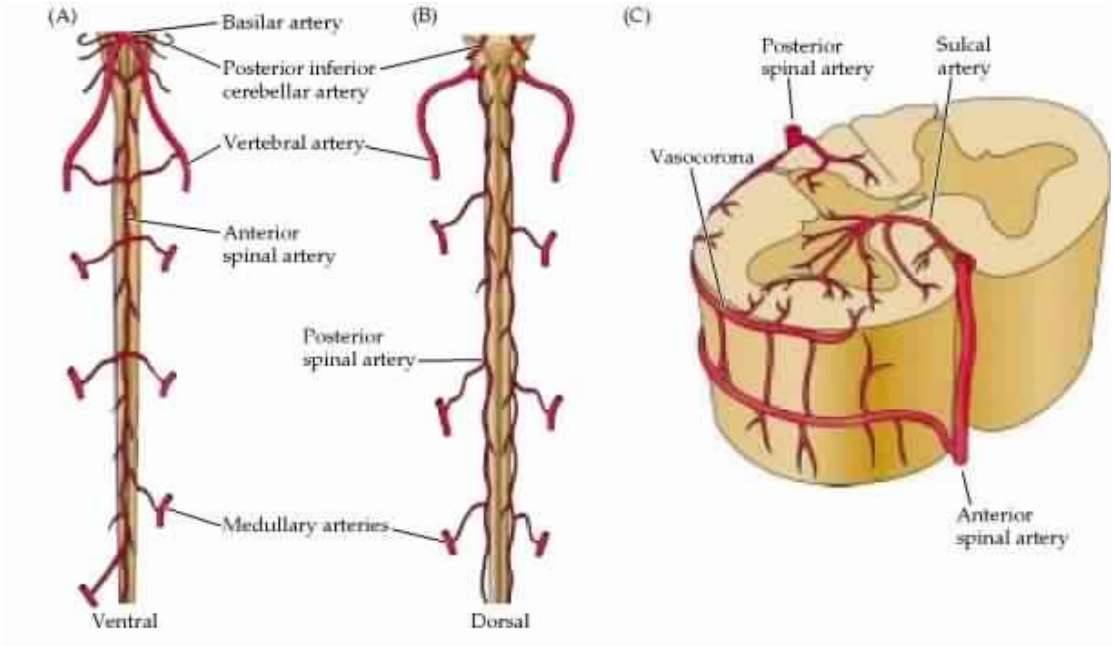
Large A fibres the most resistant to local anaesthetics, they are A5 fibres, they are more susceptible to subservient pain and temperature than C fibres, though they conduct rapidly.

Sensory Au fibers seem to be more susceptible to blocking than motor Act fib ers, though at the same velocity of conduction. This may be because sensory fibres conduct at a higher frequency.

Preganglionic, heat, pain, touch, proprioception, and motor fibres appear to be the order of sensitivity to blockade.

Blood supply of the spinal core[32]:

The principal arterial supply to the spinal cord is derived from one anterior and two posterior arteries that descend from level of foramen magnum.



Anterior spinal artery- is single in number, formed at the foramen magnum by union of branch from each vertebral artery and passes down the whole length of spinal cord. It receives communications from lumbar, and other small arteries. There are commonly 2-3 communications in cervical and thoracic region, and there is only one artery, the radicular magna (Artery of Adam Kiewicz) which is unilateral supplying lumbar enlargement. It supplies lateral and the anterior columns about 3/4 of the substance of the cord.

Posterior spinal artery— two posterior spinal arteries -one on each side. They are derived at the base of the brain directly from the vertebral artery or more often from posterior inferior cerebellar arteries. They supply the posterior one-third of the spinal cord. This supply is reinforced by spinal braches of vertebral, ascending cervical posterior intercostals, lumbar and lateral sacral arteries, which pass through the intervertebral foramina.

Venous drainage:

Anterior and posterior spinal veins drain into segmental veins in the neck, the azygous veins in the thorax, lumbar veins in the abdomen, and lateral sacral veins in

the pelvis.

Nerve supply of the meninges:

The posterior aspect of the dura and arachnoid mater contain no nerve fibres and no pain is appreciated on dural puncture. Sinovertebral nerves supplies the anterior element, each of these enters an intervertebral foramina and passes up for a 1 segment and down for 2 segements.

Cerebrospinal fluid (CSF) [32]:

The term CSF was first used in 1825 by French Physiologist F.Magandie. It is normally clear & colorless fluid that fills all the cavities and space around the CNS. It is isotonic with plasma. It is secreted mainly by choroid plexus of lateral ventricle & is reabsorbed by the arachnoid villi & granulations.

In a normal adult CSF is formed at a rate of 25 ml/hr or 600 ml/day. The replacement of total spinal fluid under ordinary normal physiological circumstances is every 6 hours.

Characteristics of CSF:

Specific gravity at 37°C 1.006 (1.003-1.009)

Volume 130-150 mL

Vol. in subarachnoid space 25 — 35 mL

Pressure 70-180 mm of water

Composition of CSF:

pH	-	7.32 (7.27 — 7.37)
Glucose	-	50-80 mg/dL
pCO2	-	48 mmHg
Bicarbonate	-	25-30 mg/mL
Cells	-	< 5 cells / mm3

Chloride	-	120- 130 mEq/L
Sodium (NA^+)	-	140-150 mEq/L
Non protein nitrogen	-	20-30mg/dL
Protein	-	15-45 mg/dL

Circulation: From the lateral ventricles CSF passes through the foramina of Munro to the third ventricles, then through the aqueduct of sylvius to the fourth ventricle and then via foramen of Magendie to cisterna magna and via two foramen of Luschka into cisterna ponti. From the fourth ventricles it also passes into central canal of spinal cord. From the central subarachnoid space, it reaches spinal subarachnoid space through the foramen magnum CSF is absorbed into cranial venous sinuses through arachnoid

Functions of CSF:

- It acts as cushion between the soft and delicate brain substance and rigid cranium.
- Drainage of metabolites.
- Nutrition and oxygen supply to nerve cells to some extent.

TECHNICAL ASPECTS[32]:

When a needle is inserted in to the subarachnoid space the following are traversed,

- Skin
- Subcutaneous tissue
- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum
- Areolar tissue or epidural space

- Spinal dura mater

The highest point of the iliac crests is usually on a line crossing the spine of L4 (in the upright position) or L4-L5 interspace (in the lateral decubitus position). This line is called the topographic line of Tuffier[33].

PHYSIOLOGY OF CENTRAL NEURAXIAL BLOCKADE.[28, 29, 34, 38]

Subarachnoid block's well recognized physiological sequels are often erroneously called complications. It is essential to make a clear difference between physiological effects of anaesthetic technique and complications that imply some damage to patients.

The various factors, which control the different effects of a spinal anaesthetic technique, are.[28, 34]

- Type of drug and amount of drug
- Solution volume
- Injection site
- Injection rate
- Specific gravity of solution - baricity and density
- Barbotage

Amount of drug:

With greater amounts of drug there is an increase in the duration, height and intensity of spinal anaesthesia. There is an upper limit to the total amount of agent that may be used regardless of the volume and it is determined by the amount of that drug which may produce neurological damage.

Type of Local anesthetic agents:

The various agents can be classified as:

1. Agents of low anaesthetic potency and short duration of action: Procaine.

2. Agents of intermediate anaesthetic potency and intermediate duration of action : Lidocaine, Mepivacaine
3. Agents of high anaesthetic potency and prolonged duration of action: Bupivacaine, Tetracaine.

Volume of solution:

Increasing the volume may increase the extent of anesthesia if the amount of d rug is maintained the same. If the total volume is less, the effect of volume augmentation is limited.

Site of injection:

When all other circumstances are constant, selecting 1 or 2 spaces greater than the usual L4-L5 inter-vertbral space offers a greater level of anaesthesia.

Rate of injection:

This may be the most significant factor in determining the height of anesthesia . The level is low with slow injections. Very rapid injections can cause anesthesia to r each the thoracic region well.The slow injection of hyperbaric solution produces adeq uate distribution and generally results in low anesthesia.The slow injection of a hypob aric solution produces greater levels of spinal anaesthesia but is of longer duration tha n the levels arising from rapid injection.

Barbotage:

The term is derived from the puddling or mixing of the French word ‘barboter’**.** This is the stirring method for increasing turbulence, mixing injected solution and increasing Sub Arachnoid Block distribution.The movement to and fro mates the injec tate in the spinal fluid and mixes the agent, to carry the agent to higher levels more enomously.

Specific gravity, Density and Baricity:

When using hyperbaric solutions in horizontal plane with patient supine, the a nesthetic will preferably travel into the lumbosacral concavity to the low points of sub arachnoid space, i.e. below L3.Hyperbaric solutions travel to the most dependent porti on of the subarachnoid space when the patient's position deviates from the horizontal. With changes in position, isobaric solutions are considered not to spread and anesthesi a levels are independent of positioning. The solution is puddling close the injection sit e.

In comparison to hyperbaric solutions, hypobaric solutions are affected by pati ent gravity and position. They are administered while patient is in prone position.

Pharmacokinetics of spinal anesthesia:

There is a fall in the concentration soon following the injection of anesthetic agent into the subarachnoid space. The reason being,

1. Dilution and mixing of CSF.
2. Diffusion and distribution to neural tissues
3. Uptake and fixation by neural tissues
4. Vascular absorption and elimination

- Through arachnoid villi
- Directly from capillary bed of parenchyma.

Initially, there is a quick reduction in drug concentration, that happens shortly afte r drug injection within 23 minutes. This is due to mixing and dilution with CSF, whic h depends on the drug injection force or rate and the volume or amount of fluid in the subarachnoid space.

The second stage of concentration reduction is due to the diffusion of the agent in the spinal fluid owing to its molecular motion. Some of the agent is absorbed in the

nervous tissue at the same time.

This absorption takes place along a gradient of concentration to 3 sites.

1. The nerve roots bathed directly by anesthetics.
2. By diffusion through the pia mater directly into the spinal cord surface.
3. Through Virchow Robin spaces into the deeper areas of the spinal cord paren chyma.

The uptake of local anesthetic from the spinal fluid and nerve fibers into the va scular compartment represents the third stage of slow decline in total concentration of agent in the spinal fluid.The significant part of the drug leaves the subarachnoid space through venous drainage, while a small part passes through tiny lymphatic channels. Very less amount or no breakdown of local anesthetic agents occurs in the CSF or in the subarachnoid space.

The various factors that affect the spread of local anesthetics include[35, 36]**:**

1. Position
2. Age
3. Height
4. Configuration of spinal column
5. CSF volume
6. Injection site
7. Spread of injected drug
8. Needle direction
9. Dose of local anesthetics
10. Baricity of local anaesthetics
11. Volume of local anesthetics
12. Technical factors

The sequence of nerve modality block[37]:

1. Vasomotor block --- skin vessels dilatation and elevated cutaneous blood flow
2. Temperature fibers --- first cold and then warmth.
3. Pain --- First pin prick fibers
4. Tactile sensation loss
5. Paralysis of Motor nerve
6. Loss of temperature discrimination
7. Pressure sensation
8. Vibratory and Proprioceptic sensation

During the recovery, return of sensations is in the inverse sequence.

The significant determinant of physiological response to spinal anesthesia is sympathetic blockade. Indirect effects of spinal anaesthesia may be regarded as a result of paralysis of sympathetic nerves.

"Effect of Spinal Anaesthesia on Various Organs"[38]:

Cardiovascular System:

The most significant physiological response to spinal anesthesia is the cardiovascular system. They are mediated by mixed autonomic denervation and greater levels of neural blockade and added vagal nerve intervention effects.

Sympathetic Denervation:

The sympathetic blockade level determines the extent of cardiovascular responses to spinal anesthesia.The higher the neural blockade level, the higher the cardiovascular parameters would change.There is a reflex increase in sympathetic activity in sympathetically intact areas in the presence of partial sympathetic blockade. The outcome is vasoconstriction that tends to compensate in sympathetically denerved regions for peripheral vasodilatation.

Arterial Circulation:

Sympathetic denervation on the arterial side of circulation results in more arter ial and physiologically significant arteriolar vasodilatation of vascular smooth muscle s.As a consequence of this total peripheral vascular resistance in normal subjects redu ces only about 15% to 18% in the presence of total sympathetic denervation provided that the cardiac output and other blood pressure determinants are maintained normal.

Venous Circulation:

After pharmacological denervation, veins and venules with only a few smooth muscles on their walls will not retain significant residual tone. They can vasodilate to the maximum.Intraluminal hydrostatic pressure determines this.Intraluminal hydrosta tic pressure is dependent on gravity on the venous sides of the circulation.If the dener vated veins are below the right atrium level, this causes the blood to flow back to the heart. Therefore, preloading to the heart depends on the patient's position during spina l anaesthesia.

Physiology of Hypotension:

The most common and immediate complication of spinal anesthesia is Hypotension.Hypotension following spinal anesthesia is predominantly the result of p reganglionic sympathetic fibers paralysis that transmits motor impulses to the peripher al vasculature's smooth muscles. Fall in B.P level was proportional to the blocked number of sympathetic fibres.

It was not understood the exact mechanism by which sympathetic blockade reduce blood pressure. Two schools of thought existed:

- One postulated that widespread arterial and arteriolar dilatation resulted in a d ecrease in peripheral vascular resistance that was sufficient to account for the vital portion of the decrease in peripheral vascular resistance.

- Others assumed that the hypotension was secondary to a reduction in cardiac p roduction due to peripheral pooling and a decline in venous blood return to he art.

While both theories are right, neither is sufficient in itself to explain all the cha nges induced by spinal anesthesia in circulatory physiology**.** The sympathectomy resu lting in spinal anesthesia technique depends on the block's height.The question left un answered at which level of arterial blood pressure is acceptable after the central neura xial block. If the blockade extends above the level of T5, the hemodynamic transition will gradually become more difficult to compensate and the blood pressure will decre ase significantly.

Hypotension develops usually during the first 15-20 minutes during spinal anaesthesia ;left untreated BP reaches its lowest level within 20-25 minutes after subarachnoid injection. For this reason, the first ½ hour of a spinal anesthesia is considered its dangerous peri od, although in some individual the initial fall in B.P may develop with alarming rate. After the BP has reached its lowest point, the systolic B.P often rises 5-10 mmHg spo ntaneously over the next 10-15 minutes, after which the roots have worn off their con centrations and remain comparatively fixed until the anesthetic nerve effect.This sligh t rise is a result of compensatory circulatory activity mediated by the blocked proporti ons of sympathetic outflow and possibly by a slight return of smooth muscle tone in t he denervated part of the peripheral vasculature.

Heart Rate:

Spinal anesthesia is typically associated with slowing of the heart rate. The degree of bradycardia can be approximately correlated with the extent of sympath etic denervation as well as the frequency with which it occurs. Marked bradycardia is most commonly noted when cardiac output and arterial B.P has considerably reduced during anaesthesia.

Bradycardia during high Spinal Anesthesia[39]:

“During spinal anesthesia, there is one factor which influences pulse rate and arterial blood pressure. A decrease in venous return results in reduction in cardiac output and cardiac output is one of the main determinants of the level of arterial blood pressure during spinal anesthesia.

Decreased venous return to the heart may induce bradycardia by one of the three mechanisms. First the hydrostatic pressure in the right heart affects heart rate through intrinsic chronotropic stretch receptors located within the wall of right atrium. These baroreceptors independent of neural connection to the central nervous system form intracardiac reflexes in which the heart rate is proportional to pacemaker stretch. The baroreceptors normally respond to a fall in blood pressure by producing a compensatory tachycardia (Marey's law) through vagal afferent and efferent pathways. Most patients under spinal anesthesia exhibits bradycardia. Thus in spinal anesthesia venous pooling in the periphery reduces stimulation of the volume receptor nerves. The result is vagal preponderance and a slowing of the heart rate. The increase in pressure in the great veins or in the right atrium produces tachycardia reflexly via stretch receptors and vice versa.

Within the walls of the ventricles there are nerve endings, which may be activated mechanically either by ventricular distension and stretching or by vigorous and rapid systolic contractions. The reflex, also called the "Bezold Jarisch reflex" arises from mechanoreceptors and chemoreceptors found primarily in the inferoposterior wall of the left ventricle. Activation of this reflex results in increased parasympathetic activity and inhibition of sympathetic activity”[39].

Cerebral Blood Flow:

Two main factors govern the cerebral blood flow. Mean arterial blood pressure

in the cerebral vessels and local blood flow resistance in cerebral vessels. Theoretic ally, spinal anesthesia may affect cerebral blood flow, altering either blood pressure or cerebrovascular resistance or both. The autoregulatory mechanism of the cerebrovasc ular system maintains cerebral blood flow in humans at steady levels in the presence of wide Variations in mean arterial blood pressure. “Cerebral blood flow will become pressure dependent until the Mean Arterial Pressure (MAP) drops below 55 mm Hg”. In the sympathetic nervous system, cerebrovascular auto-regulation is independent.

In normal persons, cerebral blood flow continues un affected even when mean arterial pressure during spinal anaesthesia declines from 90 to 60 mm hg.

The Respiratory system:

The phrenic nerve that supplies the diaphragm is derived from the anterior root, root of C3-C5, and should not be encroached into spinal anaesthesia, but phrenic paralysis may happen. Apnea may be due to medullary ischemia or in extradural blocks owing to toxic impacts of the drug. Breathing becomes quite and tranquil during spinal anesthesia.This is not only due to motor blockade, but also due to differentiation in the resp iratory center with reduction of sensory input. Lowered arterial and venous tone also diminish es the work of heart and relives any existing pulmonary congestion. The relationship of ventilation perfusion during extradural block is not significantly changed and the impact on respiratory function is comparatively low with no evidence of change in the proportion of FRC or V/Q. The exchange of pulmonary gas is preserved. Intercostal paralysis is compensated by enhanced diaphragm descent, which is facilitated by a lax abdomen.

The Gastrointestinal system:

T5-L1 sympathetic pre-ganglionic fibers are gut inhibitors. There is no impact on the esophagus, which is vagal in the innervation. The small intestine is contracted with the removal of sympathetic inhibitory impulses, the vagus being all-powerful. The sphincters are relaxed and though not more frequent, peristalsis is active. There is

enhanced pressure within the lumen of the bowel. Handling of small bowel by the surgeon may cause it to dilate, as may the injection of atropine before the operation. Due to the hypotension, nausea and vomiting can happen and generally occurs in waves that last about a minute and pass spontaneously.

Causes of Nausea and Vomiting:

1. Increased peristalsis
2. Traction on nerve endings, in particular vagus
3. The presence of bile in the stomach caused by pyloric sphincter relaxation
4. Narcotic analgesics (pre medication)
5. Psychological effects
6. Hypotension
7. Hypoxia

The Spleen:

When its sympathetic efferent fibers are paralyzed, the spleen enlarges 2-3 times in high level blocks. Following spinal anaesthesia, colonic blood supply and oxygen availability in animals are improved, perhaps a significant factor in preventing anastomotic breakdown following gut resection.

The Liver:

There are no significant effects. It is not known the degree of hypotension that affects liver function. If the liver is diseased, a reduction in MAP effects the liver blood flow and also amide anesthetics metabolism.

Endocrine system:

Spinal block delays adrenal responses to injury and trauma, so the levels of 17-hydroxy corticosteroids do not change. Spinal block suppresses the surgery and stress induced hyperglycemic response and is therefore helpful in diabetic patients.

Insulin response is increased, one should be conscious of hypoglycemia risk. IV-infused glucose is well utilized.

Genitourinary system:

Via the lower splanchnic nerve, sympathetic supply to the kidney is from T11-L1. Any effects on renal function are caused solely due to fall in blood pressure, the renal blood flow decreases but does not cease until blood pressure drops to about 80 mm Hg. These changes are temporary and disappear when Blood pressure increases again. Due to paralysis of Nervi erigenti(S2-S3), the penis is often engorged and flaccid, and this is also a favorable indication of a successful block. Post-spinal urine retention may be moderately prolonged since S2-S3 includes small autonomic fibers and their paralysis remains longer than that of larger sensory and motor fibers. The bladder must be palpated during prolonged blockade of lumbar and sacral segments so that catheterization can be done if needed. Sometimes spermatorrhoea is seen.

Uterus:

The tone of the uterus is not significantly altered during pregnancy following spinal anaethesia. The blocking of nerves from T11 results in painless labor. Due to decreased extradural space, lesser doses of local anesthetics are required in late pregnancy.

Body temperature:

Vasodilation causes heat loss, lack of sweating causes hyperpyrexia in a warm setting, catecholamine secretion is decreased hence heat loss is generated by metabolism.

Electrolyte status:

Salt and water are retained after surgery and trauma. Continuous extradural block in patients undergoing upper abdominal surgeries abolishes sodium retention

but not water retention.

THE PATHOPHYSIOLOGY OF PAIN[30-33]

Pain is defined as a sensory experience evoked by stimuli that injure or threaten to destroy tissue and more specifically is described as the perception of an aversive sensation that originates from a specific region of the body.

Psychological pain occurs when a noxious stimulus activates high threshold sensory receptors (nociceptors). This informs the body of potential or actual damage and correlates with withdrawal reflexes.

Pathological pain occurs in response to non-noxious stimulus or even in the absence of a definable stimulus. This promotes healing by avoidance of all stimuli but is truly pathological in its chronic form.

The sensory component of pain: Pain signals are received by the nociceptors at the periphery and transmitted by thinly myelinated a-delta fibers and unmyelinated C fibers.

Nociceptors:

Nociceptors are receptors that transduce noxious stimuli. Most nociceptors are free nerve endings that sense heat, mechanical pressure and tissue damage.

Types of nociceptors:

a) Mechano-nociceptors: respond to pin prick & touch
b) Silent nociceptors: responds only when inflammation occurs
c) Polymodalmechano-nociceptors: most common and responsive to excessive stress, temperature extremes and substance-generating pain.
d) Cutaneous nociceptors: available in somatic and visceral tissue.

e) Deep nociceptors: Less sensitive than cutaneous nociceptors but readily sensitized by inflammation. Dull and poorly localized pain arises from these receptors.

f) Visceral nociceptors: Generally insensitive tissues that contain mostly silent nociceptors. Brain lacks nociceptors altogether, but meningeal coverings do contain nociceptors.

A delta fibers -Only mechanically sensitive, conduct at 5-25 m/sec and transduce fast or first pain, which causes withdrawal from the source of pain.

C fibers - Conduct at less than 2m/sec and convey the messages generated by tissue damage, (slow or second pain) which may cause immobilization. They are Polymodal because they respond to noxious, thermal, mechanical and chemical stimuli.

Pain Pathways :(Fig. 6)

Pain is conducted along the three neuronal pathways that contain noxious stimuli from the periphery to cerebral cortex.

1. **First order neuron:**

Majority of these neurons send their axons into the spinal cord via the dorsal spinal root at each cervical, thoracic and sacral level. In the dorsal horn they may synapse with interneurons, sympathetic neurons and motor neurons

2. **Second order neurons:**

They synapse in the thalamic nuclei with third order neurons. Rexed divided spinal cord gray matter into 10 laminae. First six laminae make up dorsal horn, receive all afferent neural activity and represent the principal site of modulation of pain.

a) Spinothalamic tract:

(STT) Axons of most second order neurons cross the midline close to their level of origin to the contra lateral side of the spinal cord to become spinothalamic tract. This ascending tract can be divided into Lateral and Medial. Lateral STT projects mainly to the ventral-postero-lateral nucleus of thalamus and carries discriminative aspects of pain such as location, intensity and duration. The medial STT projects into medial thalamus and is responsible for mediating the autonomic and unpleasant perceptions of pain.

b) Alternate pain pathways:

a) Spinoreticular- tract it is thought to mediate arousal and autonomic response to pain.

b) Spinothalamic tract-activates hypothalamus and evokes emotional behavior to pain.

c) Spinocervical tract-ascends uncrossed to lateral cervical nucleus where it relays fibers to conventional thalamus and is an alternate pathway.

III. Third order neuron:

Sends projections through the internal capsule and corona radiata to the posterior central gyrus of the cerebral cortex. Perception and discrete localization of pain takes place in these cortical areas.

Chemical mediators of pain:

Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neuron sub serving pain. The most important of these peptides are Substance P, Calcitonin Gene Related Peptide (CGRP) and Glutamate, which have an excitatory effect on nociception of which glutamate, is the most important excitatory amino acid. GABA and glycine are the major inhibitory neurotransmitters.

Modulation of pain[40, 41]:

a) **Peripheral modulation:** Nociceptors and their neurons show sensitization after repeated stimulation and this sensitization may appear as an enhanced response to noxious stimuli.

b) Central modulation

Facilitation by at least three mechanisms:

a) Windup and sensitization of second order neurons.

b) Receptor field expansion.

c) Hyper excitability of flexion reflexes.

Preemptive analgesia[42]

The importance of peripheral and central modulation in nociception has fostered the concept of 'preemptive analgesia' in patients undergoing surgery. This may involve infiltration of the wound with LA, central neuraxial blockade or the administration of opioids to name a few.

Theories of pain:

Although the exact mechanism of pain relief is not clear, various theories have been put forward. of all the theories, the Gate control theory of pain is the most widely accepted.

Gate control theory of pain[43]:

Proposed by Melzack and Wall in 1965 and then later modified by them in 1982. They initially took into consideration the evidence of physiological specialization, central summation, patterning modulation of input and the influence of psychological factors.

The theory states that

1. A spinal gating mechanism in the dorsal horn modulates the transmission of nerve impulses from afferent fibers to spinal cord T cells.
2. The mechanism of spinal gating is influenced by the relative amount of activity in large diameter (L) and small diameter fibers, and activity in large fibers tends to inhibit transmission, thus closing the gate, while activity in small fibers tends to promote transmission, thereby opening the gate.
3. The mechanism of the spinal gating is influenced by the nerve impulse that descends from the brain.
4. A central control trigger carries precise information about the nature and location of the stimulus, which occurs rapidly. This rapid transmission makes it possible for the brain to identify, evaluate, localize and selectively modulate the sensory input before the action system is activated.
5. When the output of the spinal cord transmission (T) cells exceeds a critical level , it activates the action system in those neural areas that underline the complex sequential pattern of behavior and thereby experience characteristics of pain.

Melzack and Wall modified their theory, which includes excitatory and inhibitory links from the substantia gelatinosa to the transmission cells as well as the descending inhibitory control from the brain stem system. Melzack and Wall theories though have deficiencies, have proven to be among the most important development in the field of pain research. They also have stimulated much psychological and physiological research and have proved the development of newer approaches to pain therapy.

Effects of postoperative pain:

- Respiratory: Atelectasis, sputum retention and hypoxemia doe to ineffective cough.
- CVS: Increased myocardial oxygen demand and ischemia.
- GIT: Decreased gastric emptying, reduced gut motility and constipation.
- Genitourinary: urinary retention.
- Neuro-endocrine: Hyperglycemia, protein catabolism and sodium retention.
- Musculoskeletal: Reduced mobility, pressure sores and increased risk of Deep Vein Thrombosis.
- Psychological: Anxiety and fatigue.

PHARMACOLOGY

PREGABALIN [44,45,46]

HISTORY

"Pregabalin was formulated as an anticonvulsant in 1990. It was invented at Northwestern University in Evanston, Illinois by chemist Richard Bruce Silverman. Silverman is best known for identifying the drug Pregabalin as a possible treatment for epileptic seizures. The drug was approved in 2004 in the European Union. In December 2004, the US obtained FDA acceptance for use in the treatment of epilepsy, neuropathic & diabetes pain, and post-herpetic neuralgia. In the fall of 2005, Pregabalin emerged on the US market under the brand name Lyrica".[44]

CHEMICAL PROPERTIES

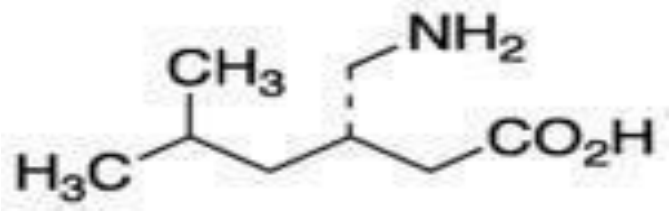
Pregabalin is described chemically as (S)-3-(amino methyl)-5-methylhexanoic Acid. It is a white to off-white, crystalline solid. It is freely soluble in water and both Basic and acidic aqueous solutions.

Molecular formula is: C8H17NO2

Molecular weight is: 159.23

PH: 7.4

The chemical structure of Pregabalin is:



MECHANISM OF ACTION

"Pregabalin is a GABAergic anticonvulsant and central nervous system (CNS) depressant. It is classified as an analog of GABA and gabapentinoid. It is a close

analog of γ-amino butyric acid (GABA) , an inhibitory neurotransmitter. Pregabalin binds to the α2δ subunit of voltage-gated calcium channels (VDCC) with high affinity. It increases extracellular levels of GABA in the brain by producing a dose-dependent increase in L-Glutamic Acid Decarboxylase (GAD), the enzyme responsible for GABA production".[45]

PHARMACOKINETICS

Absorption

Pregabalin is rapidly absorbed when administered on an empty stomach, with peak plasma concentrations occurring within one hour. Pregabalin oral bioavailability is estimated to be greater than or equal to 90% and is independent of dose.

Distribution

The volume of distribution of Pregabalin for an orally administered dose is approximately **0.56 L/kg** and is not bound to plasmaproteins.

Metabolism

Pregabalin undergoes negligible metabolism in humans. Pregabalin was found to be unchanged in roughly 98% of the radioactivity retrieved in urine in studies using nuclear medicine techniques. N-methylpregabalin is the main metabolite..

Excretion

Pregabalin is eliminated mainly by renal excretion as an unchanged drug from the systemic circulation. 73 mL/minute is the Renal clearance of Pregabalin drug.

PHARMACODYNAMICS

"Although Pregabalin is a GABA analog, it does not directly bind to GABA or benzodiazepine receptors. It neither blocks sodium channels nor is it active in opioid receptors. Gabapentinoids, like Pregabalin, are α2δ subunit modifiers that affect GABA. In contrast to the distribution of α2δ-1 and α2δ-2 subunits binding

correlates partially with GABAergic neurons. Pregabalin enhances GABA transporter protein density and increases the functional GABA transportation rate. It also increases extracellular GABA levels in the brain by producing a dose-dependent increase in L-Glutamic acid decarboxylase".[46]

INDICATIONS

Neuropathic pain associated with diabetic peripheral neuropathy (DPN) Post herpetic neuralgia (PHN), Adjunctive therapy for adult patients with partial onset seizures, Fibromyalgia, Neuropathic pain associated with spinal cord injury, Preemptive analgesia.

ADVERSE REACTION

- Angioedema
- Hyper sensitivity
- Withdrawal of Antiepileptic Drugs
- Suicidal Behavior and Ideation
- Peripheral Edema Dizziness and Somnolence
- Weight Gain

PARACETAMOL [47,48,49]

HISTORY

Paracetamol (an international name used in Europe) and Acetaminophen (an international name used in the USA) are two official names of the same chemical compound derived from its chemical name: N-acetyl-para-aminophenol and Acetyl-para-aminophenol.[47]

DESCRIPTION

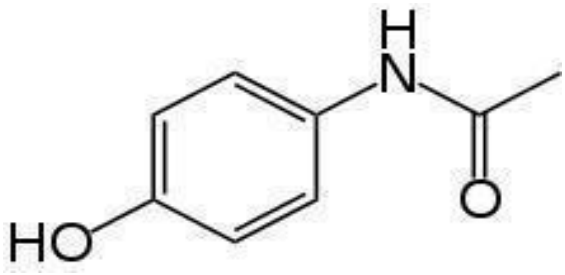
Acetaminophen is an antipyretic which is non-salicylate and non-opioid analgesic agent.

Chemical Name is N-acetyl-p-aminophenol.

Chemical formula –C8H9NO2

Molar mass -151.163 g/mol.

Its structural formula is



INDICATION

- The management of mild to moderate pain.
- The management of moderate to severe pain with adjunctive opioid analgesics and Antipyretics.

ADVERSE REACTION

Hepatic injury Skin reaction

Hypersensitivity reaction

MECHANISM OF ACTION

The mechanism of action of Paracetamol is not completely understood. Unlike NSAIDs such as aspirin, Paracetamol does not appear to inhibit the function of any cyclooxygenase (COX) enzyme outside the central nervous system. This activity does not appear to be direct inhibition by blocking an active site, but rather by reducing COX, which must be oxidized in order to function.

It also appears that Paracetamol, through the metabolite of Paracetamol, AM404, might modulate the endogenous cannabinoid system in the brain. AM404 appears to inhibit neuronal reuptake of endogenous cannabinoid / vanillin, making it more available for pain reduction. It also seems that AM404 can activate the TRPV1 (older name: vanillin receptor) directly, which also inhibits pain signals in the brain.[48]

PHARAMCODYNAMICS

Acetaminophen has antipyretic and analgesic activities. It has not been shown that single doses of acetaminophen up to 3,000 mg and repeated doses of 1,000 mg every 6th hourly for 48 hours have a significant effect on platelet aggregation. Acetaminophen has no immediate or delayed effects on small-vessel hemostasis.[49]

PHARMAOKINETICS

Distribution

The peak concentration (Cmax) occurs at the end of the 15 minute intravenous infusion of Acetaminophen. Cmax after administration of Acetaminophen is up to 70 percent greater than the same dose of oral Acetaminophen.

Excretion

"Primarily CYP2E1, to form a reactive intermediate metabolite (N-acetyl-p-benzoquinone imine or NAPQI). NAPQI undergoes rapid conjugation with glutathione with therapeutic doses and is then further metabolized to form cysteine and conjugates of mercapturic acid. Metabolites of acetaminophen are excreted mainly in the urine. Less than 5% is excreted as unconjugated (free) acetaminophen in the urine and more than 90% of the administered dose is excreted within 24 hours".[49]

Over dosage

Signs and Symptoms

In acute Acetaminophen over dosage, the most severe adverse effect is dose-dependent, potentially life threatening hepatic necrosis. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may occur.

Plasma acetaminophen concentrations > 300 mcg / mL at 4 hours after oral ingestion were associated with hepatic injury in 90 percent of patients ; minimal hepatic damage is expected if plasma concentrations < 150 mcg / mL at 4 hours or < 37.5 mcg / mL at 12 hours after ingestion.

Symptoms

Nausea, vomiting, diaphoresis, and general malaise etc.

Treatment

If an overdose of acetaminophen is suspected, obtain as quickly as possible a serum assay of acetaminophen, but not earlier than 4 hours after oral ingestion. Obtain initial Liver function test and repeat at 24-hour intervals.

Administer the N-acetyl cysteine (NAC) an antidote as soon possible.

MATERIALS AND METHODS

SOURCE OF DATA:

After obtaining institutional ethical committee clearance this prospective randomized comparative study was conducted at _____ _____ on 120 patients posted under spinal anaesthesia for lower limb surgeries from December 2017 to August 2019.

METHODS FOR COLLECTION OF DATA:

a) Design of Study: Prospective randomized comparative study.

b) Study period: The study was conducted from December 2017 to August 2019.

c) Place of study:

d) Sample size**: 120**

Sample size calculation

With Anticipated Mean Difference of VAS score between study groups as 2.5 and Anticipated SD as 3.25, the minimum sample size per group is 60 with 90% power and 1% level of significance.

Total is 120

By using the formula:

$$n = \frac{(z_{\alpha}+z_{\beta})^2 2\ SD^2}{MD^2}$$

Where Z = Z statistic at a level of significance

MD= Anticipated mean difference

SD= Anticipated Standard deviation

e) Inclusion criteria:

1. Patients from age 20-65yrs undergoing elective surgery.
2. ASA grade I and II.

f) Exclusión criteria:

4. Uncooperative and unwilling patient.
5. Hypersensitivity to drugs.
6. History of neurologic or seizure disorder.
7. Surgeries lasting for more than 3 hours.

METHODOLOGY

Informed and written consent was taken from selected patients. Following approval of institutional ethics committee, 120 patients were taken up for receiving spinal anesthesia for lower limb surgeries, all the patients were evaluated thoroughly on the previous day of the surgery. A detailed history, complete physical examination and routine investigations were done for all patients and patients were explained about visual analogue score.

120 no of patients of ASA grade I and ASA grade II were randomly allocated to two different groups of 60 each.

RANDOMIZATION: The study population of 120 with age and sex matched were randomly selected and divided by computer generated random number tables into two groups with 60 patients in each group.

GROUP PG- Received Pregabalin 150 mg orally 1 hour prior to surgery with 5ml of water.

GROUP PA- Received Paracetamol 1gm orally 1 hour prior to surgery with 5ml of water.

Patient was monitored preoperatively, for baseline pulse rate, non invasive blood pressure (NIBP) and SPO2.

Once the patient is inside the OT, IV line is secured; preloading with 10ml/kg/hr of ringer lactate was done.

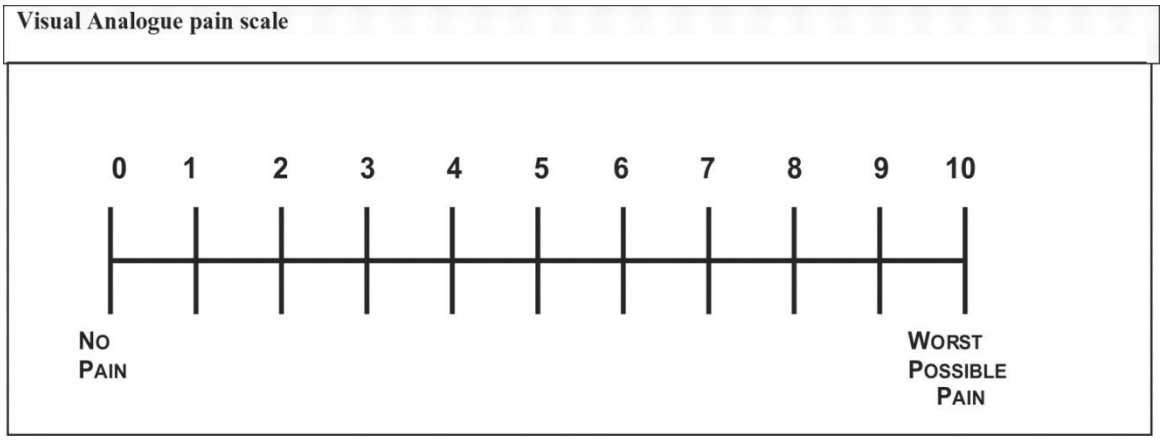
Under aseptic precautions, after painting with betadine and spirit and draping the patient, lumbar puncture at L_3-L_4 interspace using a 25/26G Quincke's spinal needle with patient in left lateral/sitting position is done. Bupivacaine heavy(0.5%) at a dose of 0.3mg/kg body weight is injected into the subarachnoid space after noting the clear free flow of CSF, with the operating table in horizontal position. Patients are turned supine immediately and are given supplemental oxygen 2-4L/min, and level of block checked. Intraoperative SPO2, pulse rate and blood pressure were monitored.

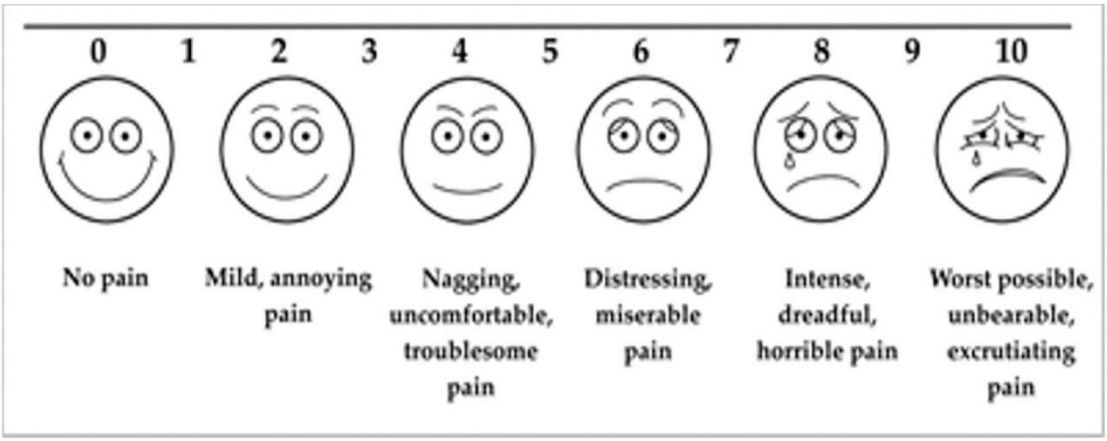
Post operative pain was assessed with using visual analogue score at 2, 4, 6, 12, 24 hours after surgery.

RESCUE ANALGESIA.

VAS consists of a 10 cm line anchored at one end by a label such as "NO PAIN" and at other end by a label "WORST PAIN IMAGINABLE" The patient simply marks the line to indicate the pain intensity and the provider then measures the length of line to mark a point scale. All the patients will be instructed about VAS and to point out the intensity of pain on the scale.

0-NO PAIN, 10-WORST PAIN.





If visual analogue score is more than 3, analgesia was given in the form of Inj Tramadol 1mg/kg. Time of first analgesic given post operatively and the total amount of analgesic given in 24 hours were noted.

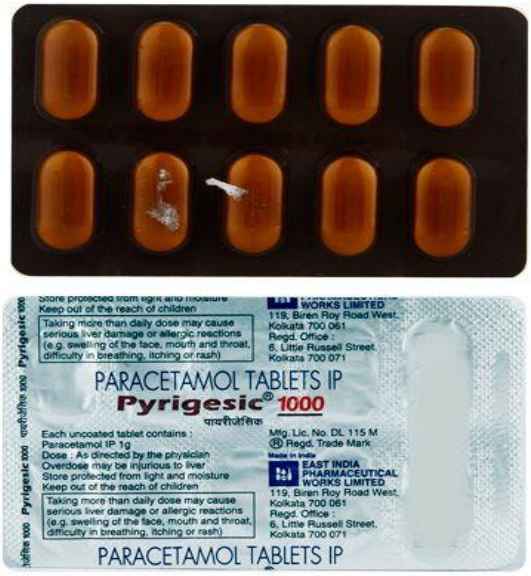
g) Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and data was analyzed by Chi square test for association, Comparison of means using t test, ANOVA and diagrammatic presentation.

DRUGS USED

1. Pregabalin

2. Paracetamol



OBSERAVTIONS AND RESULTS

TABLE 1: DISTRIBUTION OF AGE BETWEEN STUDY GROUPS

AGE(yrs)	GROUP PG		GROUP PA		p value
	N	%	N	%	
20	3	5.0%	3	5.0%	0.346
21-30	15	25.0%	12	20.0%	
31-40	14	23.3%	17	28.3%	
41-50	9	15.0%	16	26.7%	
51-60	14	23.3%	11	18.3%	
61-65	5	8.3%	1	1.7%	
Total	60	100.0%	60	100.0%	

Note: * significant at 5% level of significance ($p<0.05$)

In group PG, maximum number of patients i.e. 15(25%) were in the age group of 21-30years, whereas 12 (20%) were in the age group PA at 21-30yrs. In Group PA, maximum number of patients i.e. 17 (28.3%) were in the age group of 31-40 years, whereas 14 (23.3%) were in the age group of 31-40 years in group PG.

FIGURE 1: DISTRIBUTION OF AGE BETWEEN STUDY GROUPS

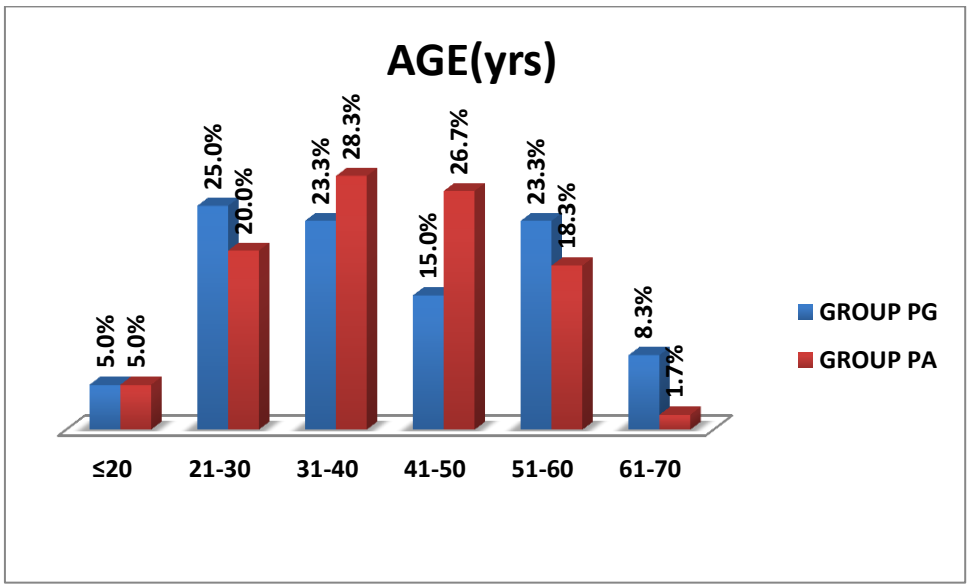


TABLE 2: MEAN AGE BETWEEN STUDY GROUPS

AGE (YRS)	GROUP PG		GROUP PA		p value
	Mean	SD	Mean	SD	
	41.70	13.96	40.23	12.62	0.547

Note: * significant at 5% level of significance ($p<0.05$)

The mean age in group PG and PA were 41.70±13.96 and 40.23±12.62 respectively and comparable between both the groups (p value-0.547).

FIGURE 2: MEAN AGE BETWEEN STUDY GROUPS

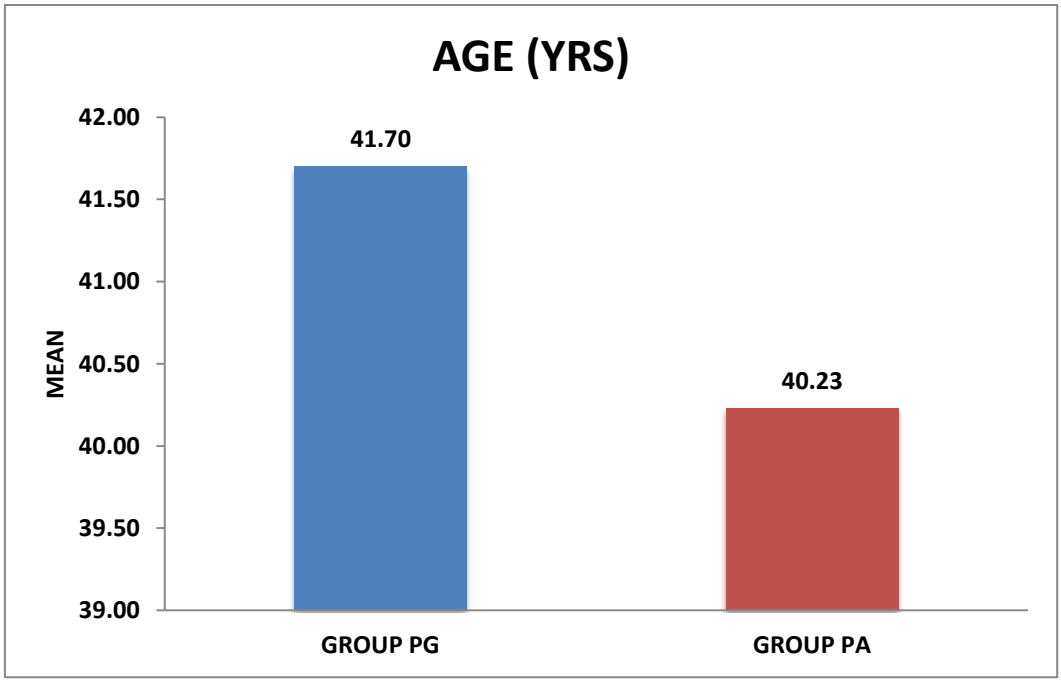


TABLE 3: DISTRIBUTION OF SEX BETWEEN STUDY GROUPS

SEX	GROUP PG		GROUP PA		p value
	N	%	N	%	
Male	51	85.0%	47	78.3%	0.345
Female	9	15.0%	13	21.7%	
Total	60	100.0%	60	100.0%	

Note: * significant at 5% level of significance (p<0.05)

The numbers of females in group PG were 9 and in group PA were 13. The number of males in group PG were 51 and in group PA were 47 (P: 0.345, P>0.05), thus the both groups were comparable statistically as far as sex is concerned.

FIGURE 3: DISTRIBUTION OF SEX BETWEEN STUDY GROUPS

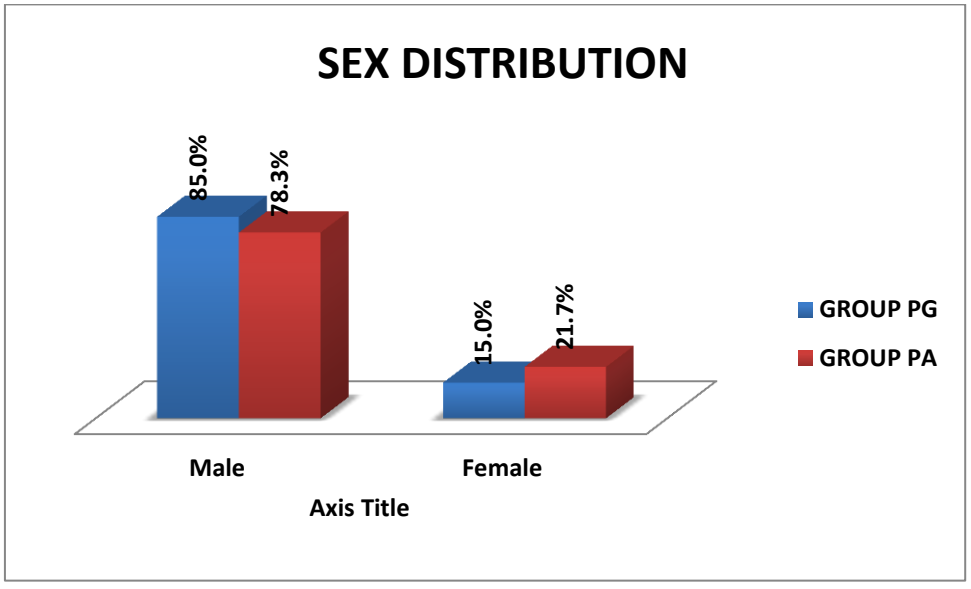


TABLE 4: DISTRIBUTION OF ASA GRADE BETWEEN STUDY GROUPS

ASA	GROUP PG		GROUP PA		p value
	N	%	N	%	
1	38	63.3%	36	60.0%	0.707
2	22	36.7%	24	40.0%	
Total	60	100.0%	60	100.0%	

Note: * significant at 5% level of significance (p<0.05)

The number of ASA grade I patients in group PG were 38 and in group PA were 36. The number of ASA grade II patients in group PG were 22 and in group PA were 24. Both groups were comparable as far as the ASA grading was concerned as the p value is 0.707 (p value>0.05).

FIGURE 4: DISTRIBUTION OF ASA BETWEEN STUDY GROUPS

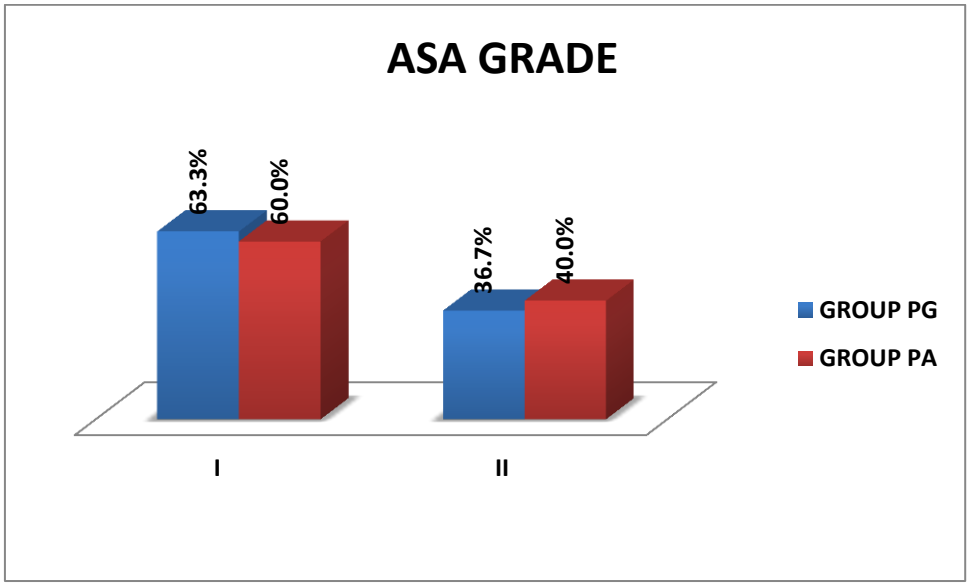


TABLE 5: DEMOGRAPHIC PROFILE OF BOTH THE GROUPS.

DEMOGRAPHIC PROFILE	GROUP PG	GROUP PA	P VALUE	SIGNIFICANCE
Age(Years)	41.70±13.96	40.23±12.62	0.547	NS
Gender(F:M)	09:51	13:47	0.345	NS
ASA Grades	38:22	36:24	0.707	NS

Note: * significant at 5% level of significance ($p<0.05$)

NS - Not Significant

TABLE 6: MEAN VAS SCORE AMONG GROUP PG

VAS	Mean	SD	p value
2HR	2.27	0.78	<0.001*
4HR	3.33	1.00	
6HR	3.40	1.03	
12HR	3.45	0.85	
24HR	3.37	0.96	
Total	3.16	1.03	

Note: * significant at 5% level of significance (p<0.05)

The Mean visual analog score among group PG was highest at 12 hrs after surgery with a value of 3.45±0.85 and lowest at 2 hrs after surgery with a value of 2.27±0.78.

FIGURE 5: MEAN VAS SCORE AMONG GROUP PG

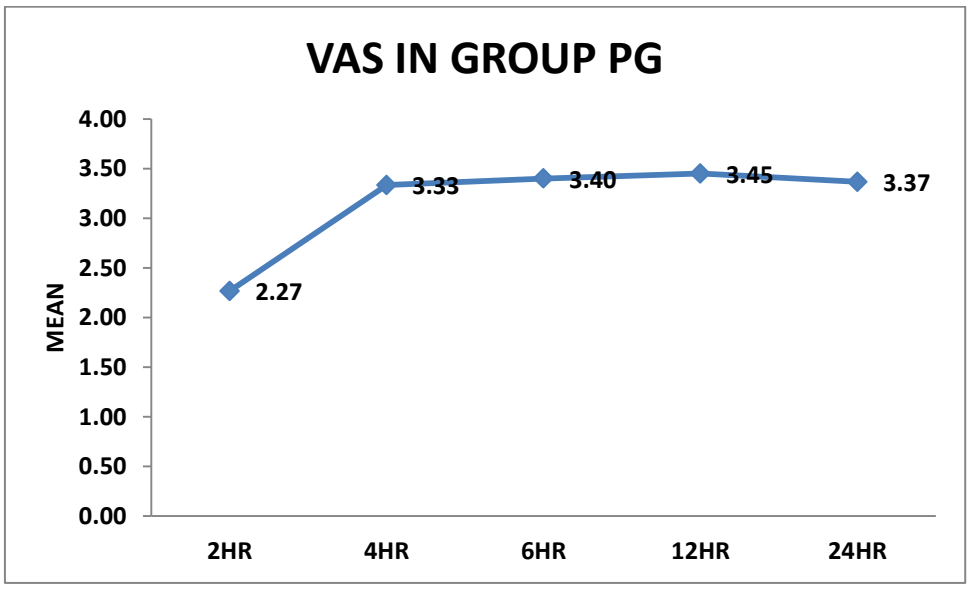


TABLE 7: MEAN VAS SCORE AMONG GROUP PA

VAS	Mean	SD	p value
2HR	2.97	0.84	<0.001*
4HR	3.62	0.74	
6HR	3.73	0.88	
12HR	3.98	0.97	
24HR	4.47	1.02	
Total	3.75	1.01	

Note: * significant at 5% level of significance (p<0.05)

The Mean visual analog score among group PA was highest at 24 hrs after surgery with a value of 4.47±1.02 and lowest at 2 hrs after surgery with a value of 2.97±0.84.

FIGURE 6: MEAN VAS SCORE AMONG GROUP PA

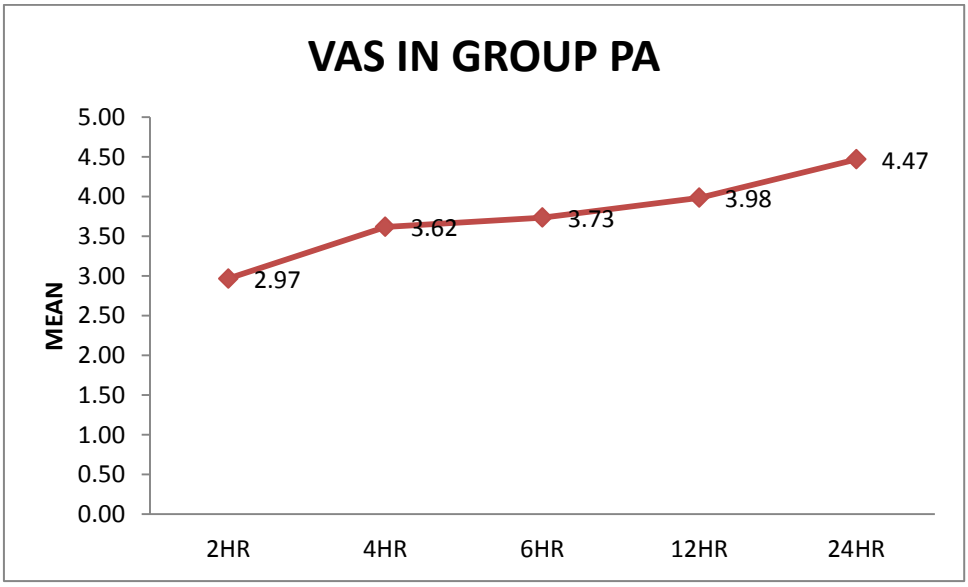


TABLE 8: MEAN VAS SCORE BETWEEN STUDY GROUPS

VAS	GROUP PG		GROUP PA		p value
	Mean	SD	Mean	SD	
2HR	2.27	0.78	2.97	0.84	<0.001*
4HR	3.33	1.00	3.62	0.74	0.081
6HR	3.40	1.03	3.73	0.88	0.059
12HR	3.45	0.85	3.98	0.97	0.002*
24HR	3.37	0.96	4.47	1.02	<0.001*

Note: * significant at 5% level of significance (p<0.05)

The mean visual analog score for group PG at 2, 4, 6, 12, and 24 hours after surgery was lower as compared to the corresponding rates for the group PA. This difference in VAS scores was significant for all times except at time 4 hrs and 6 hrs after surgery (p<0.05).

FIGURE 7: MEAN VAS SCORE BETWEEN STUDY GROUPS

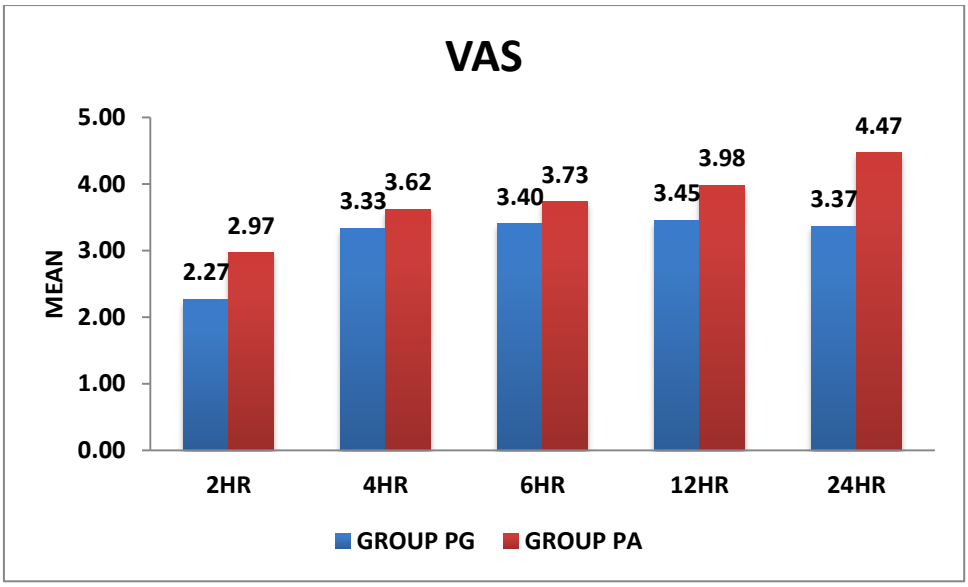


TABLE 9: TIME OF 1ST RESCUE ANALGESIA BETWEEN STUDY GROUPS.

	GROUP	Mean	SD	p value
TIME OF 1ST RESCUE ANALGESIA (HRS)	GROUP PG	4.3	1.2	<0.001*
	GROUP PA	3.3	1.1	

Note: * significant at 5% level of significance (p<0.05)

The mean time of 1st rescue analgesia for group PG was 4.3±1.2 Hrs and for group PA it was 3.3±1.1 Hrs. The time required for first rescue analgesia in group PA was early compared to group PG and which was statistically significant (p value less than <0.05).

FIGURE 8: TIME OF RESCUE 1ST ANALGESIA E BETWEEN STUDY GROUPS

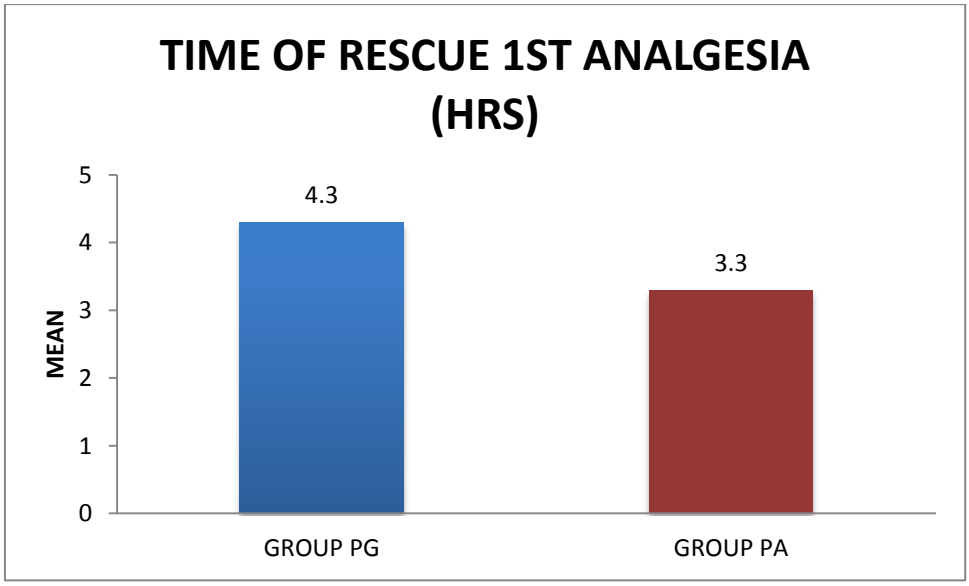


TABLE 10: TOTAL NUMBER OF RESCUE ANALGESIA IN 24 HOURS BETWEEN STUDY GROUPS

	GROUP	Mean	SD	p value
TOTAL NUMBER OF RESCUE ANALGESIA IN 24 HOURS	GROUP PG	1.6	0.6	<0.001*
	GROUP PA	2.9	0.7	

Note: * significant at 5% level of significance (p<0.05)

The mean number of total rescue analgesia in 24 hrs for group PG was 1.6±0.6 and for group PA was 2.9±0.7. The total number of rescue analgesia requirement was more in group PA compared to group PG and which was statistically significant (p value less than <0.05).

FIGURE 9: TOTAL NUMBER OF RESCUE ANALGESIA IN 24 HOURS BETWEEN STUDY GROUPS

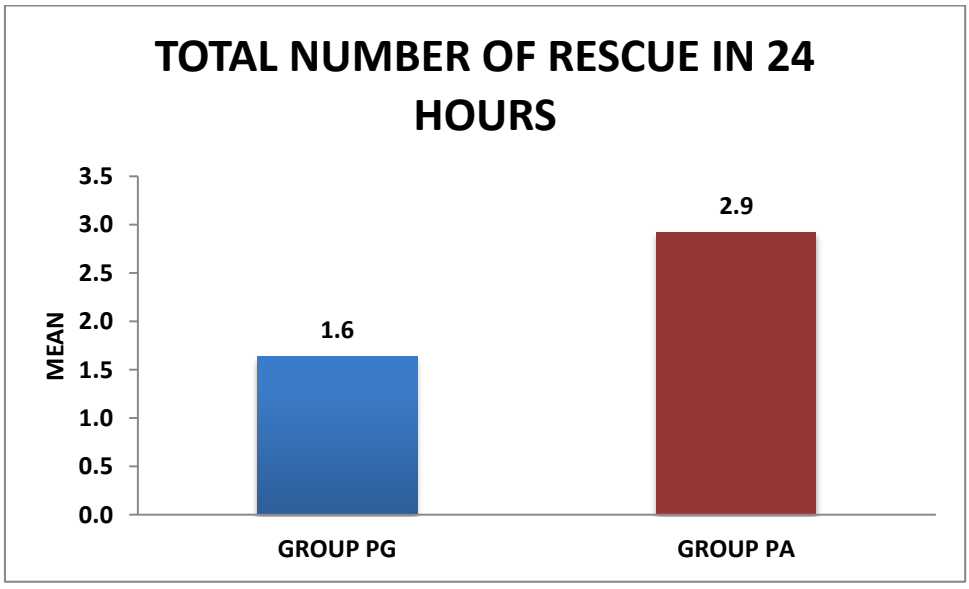


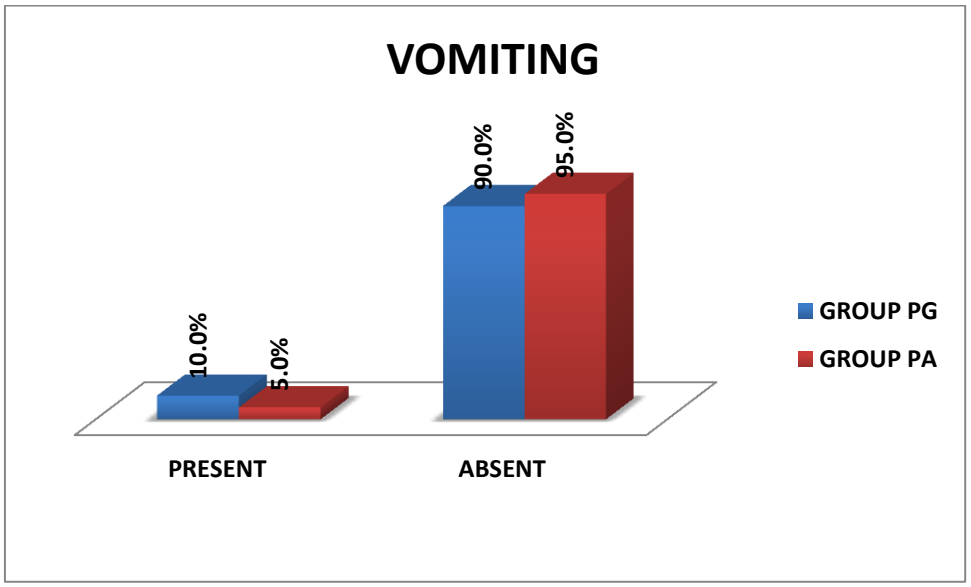
TABLE 11: COMPARISON OF VOMITING BETWEEN STUDY GROUPS

VOMITING	GROUP PG		GROUP PA		p value
	N	%	N	%	
PRESENT	6	10.0%	3	5.0%	0.298
ABSENT	54	90.0%	57	95.0%	
Total	60	100.0%	60	100.0%	

Note: * significant at 5% level of significance (p<0.05)

Group PG had higher episode of vomiting compared to group PA but was not statically significant as p value is 0.298.

FIGURE 10: COMPARISON OF VOMITING BETWEEN STUDY GROUPS



DISCUSSION

The study was a prospective randomized comparative study conducted on 120 patients under spinal anesthesia for lower limb surgeries at _____ _____from December 2017 to August 2019.

The goal of this study was to assess the efficacy of pre-emptive Pregabalin and Paracetamol for postoperative analgesia. We also assessed the adverse effect of both and compared effects of both drugs when administered 1 hour before the induction of spinal anaesthesia. The dosage of Pregabalin and Paracetamol was decided after careful review of the various studies mentioned in the review of literature.

After written and informed consent, patients were allotted into two different groups by computer generated randomization. One hour before surgery the drug was administered with 5ml of water.

The patient in group PG received Pregabalin 150mg and in group PA received Paracetamol 1000mg.

During the pre-anaesthetic evaluation all the patients were taught the visual analogue scale (VAS).

Vitals like HR, SBP and DBP were monitored initially and intra operatively. In the post operative period, the time to first rescue analgesic and total analgesic consumption assessed.

DEMOGRAPHIC DATA

Demographic data like age, gender, male to female ratio and ASA status was taken into consideration.

In our study mean age distribution in group PG was 41.70±13.96 and in group PA 40.23±12.62. The age distribution was higher in group PG compared to group PA

but was statistically not significant. The groups were comparable.

Comparison of gender distribution among the two groups shows that males were higher in both the groups when compared to the female, which was statistically not significant. (Male: female - 85%:15% and 78.3%:21.7% in group PG and group PA respectively).

ASA status in both groups were comparable.

These findings were similar to the study by Bon Sebastian *et al.,* (2016)[18] who had 90 patients aged between 18 and 60 years old of both sex of American Society of Anaesthesiologists (ASA) physical status I and II undergoing lower limb orthopedic surgeries under spinal anaesthesia. Results of the their study too, did not show significant difference in the demographic data of the groups of patients as regard age, male to female ratio, ASA physical status.

POSTOPERATIVEANALGESIA

Time requirement of first rescue analgesia with group PG mean duration was of 4.3±1.2 hrs and group PA mean duration 3.3±1.1 hrs and p values < 0.001which statistically significant. It shows Pregabalin has better post-operative analgesia compared to Paracetamol.

Total number of rescue analgesia with group PG was 1.6±0.6 and compared to group PA which was 2.9±0.7, which is statistically significant with p values <0.01. It shows that requirement of total dose of rescue analgesia is less with Pregabalin group compared to Paracetamol group.

This finding was similar to the study by Esmat *et al.,* (2015)[8] who found that first rescue analgesia requirement in Paracetamol group was 27.5min and for Pregabalin 150mg and Pregabalin 300mg group it was 164 min and 166 min respectively.

VISUAL ANALOGUE SCORE

Group PG has significantly less VAS score then group PA for 24 hours of Post operative period**.** The mean visual analog score for group PG at 2, 4, 6, 12, and 24 hours after surgery was lower as compared to the corresponding rates for the group PA. This difference in VAS scores was significant for all times except at time 4 hrs and 6 hrs after surgery ($p<0.05$).

Similarly in the study by Mohamed Ommid *et al.,* (2015)[11] who found that there was no difference observed in the first analgesic requirement time values between the two groups ($p>0.05$). A statistically significant decrease was observed in the VAS scores of the Pregabalin group at 1, 4, 12 and 24 hours after surgery ($p<0.005$). Total morphine consumption in the Pregabalin group was statistically significantly lower than in the control group at 8, 12 and 24 hours after surgery ($p<0.005$). No significant difference was observed between the two groups regarding side effects during the first postoperative 24 hours ($p>0.05$).

POST OPERATIVE VOMITING

In our study incidence of post-operative nausea and vomiting was not significant in either group, but in comparison to group PG (6 patients) has higher incidence of vomiting compared to group PA (3 patients). Group PG had higher episode of vomiting compared to group PA but was not statically significant as p value is 0.298.

According to Joon Ho Kim *et al.,* (2014)[9], study the incidences of PONV were similar in both groups (P=0.666), and the incidence of sedation was higher in the placebo group (P=0.022). Multivariate analysis on sedation scores could not be performed to correct for the use of additional analgesics because no patient complained about sedation in the Pregabalin group. The incidence of PONV was low, and there were no sedation scores of 2 and 3 in either group.

Our study found that the Pre-emptive administration of Pregabalin and Paracetamol has better post-operative analgesia and of longer duration, reduces the requirement of rescue analgesia.

The main findings of our study were in accordance with the studies done by Ibrahim M *et al.,* Jon Ho Kim *et al.,* Mohammed Hamid *et al.,* Prashanth Gotham RJ SK *et al.,* Anitha Kumari *et al,.* who found that administration of pre-emptive Pregabalin and Paracetamol improves the post- operative analgesia**.**

SUMMMARY

Preemptive analgesia helps to reduce postoperative pain by causing the central nervous system plasticity and sensitization before nociception stimulus produced by surgery. Effective post-operative pain management increases the patient satisfaction, early mobilization, and reduces hospital stay.

In this study, we compared and assessed the efficacy of preemptive Pregabalin and Paracetamol in terms of post-operative analgesia and adverse effect in patients undergoing spinal Anesthesia for lower limb surgeries.

In this study, we found that:

The demographic profile was comparable in both groups.

VAS score lower in Pregabalin group and duration of analgesia was longer.

Requirement of total dose of rescue analgesia is lower in Pregabalin group.

First dose of rescue analgesia requirement is much later in Pregabalin group.

Incidence of post-operative nausea vomiting higher in Pregabalin group, but not deleterious, No other significant adverse effect.

LIMITATIONS OF THE STUDY

1. Our study uses 60 patients per group, it was felt that the sample size is small. Larger the sample group would help validate the finding further.
2. If the duration of surgery was prolonged the drugs were not found to be effective in reducing post-operativeanalgesia.
3. VAS score and time for rescue analgesia, though corresponding, and evaluation of comfort of patient could have been enhanced by questionnaires on postoperative analgesia pain relief.
4. Pregabalin cause sedation in postoperative period, type and severity of sedation have not been assessed in the study.

5. Plasma concentration would have measured the both Pregabalin and Paracetamol group to correlate the findings.
6. Post operative hemodynamic variations have not been assessed in the study.

CONCLUSION

Based on the finding of the study, we can conclude that pre-operative administration of oral Pregabalin 150mg was an effective and a safe adjuvant for acute pain after surgery compared to oral Paracetamol 1000 mg.

Pregabalin reduces the postoperative pain score and total analgesic consumption and there were no other significant side effects in the postoperative period.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

ANNEXURE

SAMPLE INFORMED CONSENT FORM

TITLE OF THE PROJECT:"COMPARISON OF EFFICACY OF ORAL PREGABALIN AND ORAL PARACETAMOL AS PRE-EMPTIVE ANALEGESICS IN PATIENTS RECEIVING SPINAL ANAESTHESIA FOR LOWER LIMB SURGERIES".

PRINCIPAL INVESTIGATOR :

GUIDE :

PURPOSE OF RESEARCH:

I have been informed that this study is: – "**COMPARISON OF EFFICACY OF ORAL PREGABALIN AND ORAL PARACETAMOL AS PRE-EMPTIVE ANALGESICS IN PATIENTS RECEIVING SPINAL ANAESTHESIA FOR LOWER LIMB SURGERIES.**

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study.

PROCEDURE:

I understand that I will be participating in the study: **"– COMPARISON OF EFFICACY OF ORAL PREGABALIN AND ORAL PARACETAMOL AS PRE-EMPTIVE ANALGESICS IN PATIENTS RECEIVING SPINAL ANAESTHESIA FOR LOWER LIMB SURGERIES".**

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain while receiving spinal anaesthesia and I understand that necessary measures will be taken to reduce these complications as and when they arise.

BENEFITS:

I understand that my/my wards participation in this study will help in finding out appropriate medication for pre-emptive analgesia between pregabalin and paracetamol under spinal anaesthesia to controll pain post operatively.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. _____ is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me to keep for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that _____ will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Date:

(Guide) (Investigator)

STUDY SUBJECT CONSENT STATEMENT:

I confirm that ——————————has explained to me the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience, in my own language.

I have been explained all the above in detail in my own language and I understand the same. Therefore I agree to give my consent to participate as a subject in this research project.

_____ _____

(Participant) Date

_____ _____

(Witness to above signature) Date

PROFORMA

STUDY: "COMPARISON OF EFFICACY OF ORAL PREGABALIN AND ORAL PARACETAMOL AS PRE-EMPTIVE ANALGESICS IN PATIENTS RECEIVING SPINAL ANAESTHESIA FOR LOWER LIMB SURGERIES".

Serial No. Group [PG] Group [PA]

Name: I.P. No. :

Age : Hospital:

Sex: DOA: DOS:

Preoperative diagnosis:

Proposed surgery:

PRE- ANESTHETIC EXAMINATION

Chief Complaints:

Past History:

Presence of any co-morbid condition – DM/ HTN/ IHD/ CVD/Asthama/ Bleeding disorders:

Drug allergy/ Any other:

Previous anesthetic exposure:

Present medication/ Previous drug therapy:

Family History:

General Physical Examination:

Pallor/ Icterus/ Cyanosis/ Clubbing/ Lymphadenopathy/ Pedal edema

Pulse rate: Blood Pressure:

Respiratory rate: Weight:

Temperature:

Teeth:

Jaw movement:

Mallampatti grade:

Systemic Examination :

Cardiovascular system: Central Nervou system:

Respiratory system: Others:

INVESTIGATIONS:

Hemoglobin:	TC:	Random Blood Sugar:
Blood Urea:	Serum.Creatinine:	Urine routine:
Total bilirubin:	Platelet count:	Blood group/Rh typing:
SGOT/ SGPT:	Serum Electrolytes:	BT/ CT:
X-Ray chest:	ECG:	ECHO:

Pre-operative baseline

HR:

BP:

Premedication:

ASA Grade:

Anesthetic Technique: SPINAL ANAESTHESIA

Drugs and Dosages:

Duration of surgery:

Adverse effects (If any):

INTRA OPERATIVE MONITORING AFTER 30 MIN OF SUB-ARACHNOID BLOCK:

PR: BP:

POST OPERATIVE MONITORING:

1. The time lapse between the operation and the first demand of analgesics by the patient :
2. The intensity of post operative pain on the visual analogue scale (VAS) at the time first demand of analgesia :
3. The total dose of analgesia required for 24 hours in the form of tramadol (1mg/kg) noted :

	GROUP - PG					**GROUP - PA**					
Time of request of analgesic i,e tramadol 1mg/kg(in hours)	**2**	**4**	**6**	**12**	**24**		**2**	4	**6**	**12**	**24**
Intensity of pain recording at the time of request of analgesia(VAS score)						VAS score					

Date:-

Place:-Vijayapur Investigator:-

Guide: -

KEY TO MASTER CHART

ASA	-	American society of anesthesiology
VAS	-	Visual Analogue Scale
IP NO	-	In-patient number
PG	-	Pregabalin group
PA	-	Paracetamol group
PONV	-	Post operative nausea vomiting
HR	-	Hours

MASTER CHART

							VISUAL ANALOG SCORE					PONV
SL.NO	**NAME**	**IP NO**	**GROUP**	**AGE**	**SEX**	**ASA**	**2HR**	**4HR**	**6HR**	**12HR**	**24HR**	**EPISODE**
1	UMESH	41978	PG	30	M	1	2	2	4	4	3	ABSENT
2	MALLAPPA	42096	PG	40	M	2	1	2	3	4	2	ABSENT
3	BASAYYA	43044	PG	55	M	2	3	3	5	3	6	ABSENT
4	GURAPPA	18541	PG	24	M	1	2	5	3	3	2	ABSENT
5	BASAVARAJ	19693	PG	29	M	1	1	3	4	3	3	ABSENT
6	MAHANTESH	20583	PG	32	M	1	2	3	6	3	3	ABSENT
7	PUTALABAI	20483	PG	55	F	1	2	4	3	5	3	ABSENT
8	GURUSAGARI	21539	PG	64	F	2	3	5	3	3	2	**PRESENT**
9	PANDAPPA	42088	PG	42	M	2	2	4	3	5	2	ABSENT
10	MAHANTESH	42319	PG	51	M	1	2	4	3	5	3	ABSENT
11	KARBASAPPPA	41397	PG	64	M	2	2	3	4	3	6	**PRESENT**
12	VINOD	9793	PG	20	M	1	2	4	3	5	3	ABSENT
13	PONU	7857	PG	64	M	2	3	5	3	4	3	ABSENT
14	KALLAPPA	40326	PG	35	M	1	1	2	5	3	3	ABSENT
15	SIDDAROOD	21462	PG	23	M	1	1	5	3	3	3	ABSENT
16	DAYAWWA	41886	PG	60	F	2	2	3	4	3	6	ABSENT
17	MADHU	9092	PG	28	M	1	1	2	3	5	3	**PRESENT**
18	DAMODAR	9305	PG	28	M	1	2	4	3	5	3	ABSENT
19	SIDDAPPA	9966	PG	28	M	1	2	4	2	4	2	ABSENT
20	KIRAN	6942	PG	22	M	1	2	3	5	2	3	ABSENT
21	TAMMAYYA	10113	PG	36	M	1	4	2	2	3	4	ABSENT
22	ANAND	18396	PG	20	M	1	4	2	3	4	2	ABSENT

23	YALLAPPA	18331	PG	24	M	1	4	3	3	4	3	ABSENT
24	PARASU	19177	PG	30	M	1	2	5	2	4	4	ABSENT
25	GOLLALAPPA	42798	PG	36	M	1	1	5	3	4	3	ABSENT
26	MAHABOOB	8687	PG	54	M	1	2	4	2	3	3	ABSENT
27	SHIVAPPA	18237	PG	47	M	1	4	2	5	2	3	ABSENT
28	SANJU	7998	PG	35	M	1	2	4	2	4	3	ABSENT
29	AMARAPPA	40298	PG	60	M	2	2	5	2	4	3	ABSENT
30	DANAMMA	41007	PG	63	F	2	2	2	4	2	5	ABSENT
31	SADDAM	41150	PG	20	M	1	2	3	3	4	3	ABSENT
32	KASHIBAI	40247	PG	54	F	2	2	4	2	3	6	ABSENT
33	SUDEEP	41543	PG	27	M	1	2	3	5	2	3	**PRESENT**
34	SHIVANAND	42036	PG	28	M	1	2	5	2	3	3	ABSENT
35	SANJEEVKUMAR	43364	PG	40	M	2	2	3	5	2	3	ABSENT
36	PREMSINGH	42921	PG	53	M	2	2	3	4	3	5	ABSENT
37	DATTANNA	5433	PG	60	M	1	2	2	3	3	3	ABSENT
38	BASVANTRAY	6782	PG	60	M	2	3	4	3	2	4	ABSENT
39	SANTOSH KUMAR	6605	PG	46	M	1	2	2	2	3	4	**PRESENT**
40	NINGAPPA	6329	PG	50	M	1	2	3	5	3	4	ABSENT
41	ELAI	27217	PG	46	M	1	2	2	4	4	3	ABSENT
42	KASHINATH	23290	PG	60	M	2	2	4	3	3	4	ABSENT
43	TAYAMMA	7146	PG	28	F	1	2	3	3	4	3	ABSENT
44	DURGAPPA	6596	PG	40	M	1	3	3	4	3	4	ABSENT
45	BALAPPA	27764	PG	60	M	2	2	4	3	3	4	**PRESENT**
46	FIROZ KHAN	7759	PG	34	M	1	2	2	3	4	4	ABSENT
47	PANDAPPA	7488	PG	30	M	2	2	3	4	3	3	ABSENT

48	NAGRAJ	13125	PG	35	M	1	3	4	3	3	3	ABSENT
49	PUTALABAI	13956	PG	60	F	2	2	3	4	3	4	ABSENT
50	RAJSHEKHAR	15841	PG	43	M	2	4	2	3	4	3	ABSENT
51	SHRIKANT	11723	PG	40	M	1	2	3	3	5	3	ABSENT
52	IRAPPA	17103	PG	25	M	1	2	3	3	4	3	ABSENT
53	BASALINGAMMA	13437	PG	50	F	2	3	4	3	4	3	ABSENT
54	SHANTANGOUDA	14549	PG	45	M	1	2	4	3	3	4	ABSENT
55	PARVEEN	15136	PG	35	F	1	2	3	4	3	4	ABSENT
56	BHIMARAY	14029	PG	32	M	1	4	2	4	3	3	ABSENT
57	NIMBANNA	15273	PG	62	M	2	2	3	6	4	3	ABSENT
58	GULABSINGH	16078	PG	39	M	1	3	4	3	4	3	ABSENT
59	SHRISHAIL	16146	PG	50	M	2	3	3	5	4	3	ABSENT
60	RAJSHEKHAR	15841	PG	54	M	2	3	5	2	2	3	ABSENT
1	PARASHURAM	18049	PA	35	M	2	2	4	4	4	5	ABSENT
2	ARJUN	42266	PA	40	M	1	4	3	5	3	4	ABSENT
3	MAHANANDAYYA	8972	PA	64	M	2	3	4	3	4	3	ABSENT
4	GOLAPPA	18048	PA	39	M	1	2	4	3	4	4	ABSENT
5	GURANNA	18733	PA	54	M	1	4	3	5	2	5	**PRESENT**
6	SANJU	41063	PA	35	M	2	2	4	3	4	5	ABSENT
7	HARISHCHANDRA	41289	PA	41	M	2	2	5	3	5	3	ABSENT
8	SHAKUNTALA	41546	PA	42	F	1	3	4	2	5	5	ABSENT
9	KRISHNA	37678	PA	48	M	2	4	2	4	4	5	ABSENT
10	MAHADEVI	41830	PA	45	F	2	4	3	3	5	4	ABSENT
11	SURESH	43425	PA	40	M	1	3	5	3	5	3	ABSENT
12	ELLAPPA	17685	PA	38	M	2	3	4	3	6	3	ABSENT

13	MAHANTESH	43092	PA	56	M	2	3	3	5	6	7	ABSENT
14	IRAWWA	18783	PA	60	F	2	4	3	5	3	5	ABSENT
15	TIRUPATHI	42527	PA	40	M	1	4	3	5	6	4	ABSENT
16	NEMU	19925	PA	60	M	2	4	3	5	3	5	ABSENT
17	KRISHNAPPA	20631	PA	40	M	1	3	4	3	5	5	ABSENT
18	DHONDIRAM	20875	PA	48	M	2	3	5	4	5	4	ABSENT
19	RAJKUMAR	41677	PA	43	M	2	3	4	2	4	5	ABSENT
20	VITTALSINGH	42014	PA	38	M	1	2	4	3	3	4	ABSENT
21	KHAJABEE	42075	PA	40	F	1	3	3	5	3	4	ABSENT
22	DUNDAWWA	21546	PA	50	F	2	3	4	3	4	5	ABSENT
23	JAGADISH	17543	PA	35	M	1	3	3	5	3	4	ABSENT
24	SHIVAPUTRA	20950	PA	55	M	2	4	3	5	4	6	ABSENT
25	RABIYA	40854	PA	44	F	1	4	3	4	3	5	ABSENT
26	PARASHURAM	42838	PA	35	M	1	1	2	4	2	4	ABSENT
27	SRIKANT	43529	PA	22	M	1	3	4	3	4	4	ABSENT
28	SHIVAYYA	9299	PA	20	M	1	2	4	3	5	4	**PRESENT**
29	GOURISH	10201	PA	28	M	1	4	3	3	4	3	ABSENT
30	GURUNINGA	17851	PA	60	M	2	4	5	4	3	4	ABSENT
31	AMASIDDA	8833	PA	32	M	1	2	3	4	5	6	ABSENT
32	RAJSHEKHAR	5398	PA	45	M	1	2	4	3	4	4	ABSENT
33	SHARANBASAPPA	3183	PA	20	M	1	3	4	3	5	4	ABSENT
34	SANGANBASAMMA	6160	PA	53	F	2	3	5	4	4	4	ABSENT
35	MALLAPPA	7331	PA	60	M	2	4	3	4	3	7	ABSENT
36	YALLAWWA	24837	PA	50	F	2	3	4	3	5	4	ABSENT
37	SHRISHAIL	6330	PA	25	M	1	3	5	3	4	5	ABSENT

38	YAMANAPPA	7503	PA	21	M	1	3	4	2	3	6	ABSENT
39	VIDYAVATI	7378	PA	22	F	1	2	4	3	3	4	ABSENT
40	SUBHASH	7688	PA	37	M	1	3	4	4	3	5	ABSENT
41	GANGABAI	7520	PA	57	F	2	4	2	4	3	5	ABSENT
42	SAYANNA	7654	PA	40	M	1	1	3	4	4	3	ABSENT
43	SUBHAS	13639	PA	43	M	1	3	4	3	5	5	**PRESENT**
44	MOSHIN	13935	PA	21	M	1	1	3	4	4	4	ABSENT
45	VIJAYKUAR	12756	PA	37	M	1	3	4	3	4	3	ABSENT
46	GOPAL	13957	PA	35	M	1	4	3	5	4	6	ABSENT
47	SHARANAWWA	24765	PA	60	F	2	2	4	3	5	4	ABSENT
48	TUNGAWWA	25607	PA	50	F	2	3	4	4	4	5	ABSENT
49	GURUBASAPPA	13789	PA	46	M	2	4	3	5	3	4	ABSENT
50	SAIBANNA	14987	PA	45	M	2	2	3	4	3	5	ABSENT
51	NAGARAJ	13956	PA	42	M	1	3	4	3	4	4	ABSENT
52	SHARANBASSU	15699	PA	22	M	1	2	3	4	3	6	ABSENT
53	DAVALA	15502	PA	48	M	1	4	3	5	3	4	ABSENT
54	SUBHASH	15705	PA	22	M	1	3	4	5	4	4	ABSENT
55	MALLAPPA	16273	PA	29	M	1	2	4	3	4	5	ABSENT
56	PARVATI	15206	PA	60	F	2	3	4	5	4	3	ABSENT
57	BHIMARAYA	17021	PA	20	M	1	4	3	4	4	7	ABSENT
58	RAVI	24838	PA	29	M	1	3	4	3	6	4	ABSENT
59	SADHAM	24527	PA	21	M	1	3	3	4	5	3	ABSENT
60	SHRIKANTH	23542	PA	24	M	1	3	4	4	3	4	ABSENT