OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF ISOBARIC ROPIVACAINE 0.75% WITH DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES

BY

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DISSERTATION SUBMITTED TO THE

SUMANDEEP VIDYAPEETH, PIPARIA, VADODARA

In partial fulfillment

of the requirements for the degree of M.D.

in

ANAESTHESIOLOGY

Under the Guidance of

Dr. JAYSHRI DESAI (PROF.)

(M.D)

DEPARTMENT OF ANAESTHESIOLOGY

SBKS MEDICAL INSTITUTE & RESEARCH CENTRE,

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YEAR 2014-2017

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SUMANDEEP VIDYAPEETH
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DATE 30.3.15
SIGN.:

Ref: Your study synopsis entitled "Observational study to compare the effect of isobaric Ropivaicaine 0.75% with Dexmedetomidine and clonidine as an adjuvant in spinal anaesthesia in lower limb and lower abdominal surgeries" Submitted to the SV IEC for approval.

Sub: Approval for conducting the referenced study

Dear Dr. Ashish,

The Sumandeep Vidyapeeth Institutional Ethics Committee (SV IEC) is in receipt of your above mentioned study document and as the research study classifies in the minimal risk category; as recommended by HRRP SBKS MI&RC. The SV IEC approves your study to be conducted in the presented form.

The approval remains valid for a period of 1 year. In case the study is not initiated within one year, the Ethics Committee expects to be informed about the reason for the same and a fresh approval will have to be obtained subsequently.

The Sumandeep Vidyapeeth Institutional Ethics Committee expects to be informed about the progress of the study (every 6 months), any Serious Adverse Event (SAE) occurring in the course of the study, and if any changes are made in the protocol or patient information/informed consent the SVIEC needs to be informed about this in advance and an additional permission is required to be taken. The SV IEC also requires you to submit a copy of the final study report.

Dr. Niraj Pandit
Sumandeep Vidyapeeth
Institutional Ethics committee

SUMANDEEP VIDYAPEETH
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Date: 21st Oct 2016

STUDY COMPLETION CERTIFICATE

This is to certify that your study synopsis entitled: "Observational study to compare the effect of isobaric Ropivaicaine 0.75% with Dexmedetomidine and clonidine as an adjuvant in spinal anaesthesia in lower limb and lower abdominal surgeries" Research Project was done by **"Dr. Ashish Tyagi"** (3rd year Resident, Dept of Anaesthesiology, S.B.K.S MI & RC, Dhiraj Hospital, Piparia, Waghodiya road, Vadodara-391760, Gujarat) and it was conducted to the satisfaction of the Sumandeep Vidyapeeth Institutional Ethics committee.

Dr. Niraj Pandit
Member Secretary
SV Institutional Ethics committee

SUMANDEEP VIDYAPEETH
INSTITUTIONAL ETHICS COMMITTEE
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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation/thesis entitled **OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF ISOBARIC ROPIVACAINE 0.75% WITH DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES** is a bonafide and sincere research work performed by me under the guidance of **DR. JAYSHRI DESAI.**

Date: **Signature of the Candidate**

Place: **Dr. Ashish Tyagi**

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF ISOBARIC ROPIVACAINE 0.75% WITH DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES** is a bonafide research work done by **Dr. Ashish Tyagi** under my guidance and in partial fulfillment of the requirement for the degree of **M.D. Anaesthesiology.**

Date:
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ENDORSEMENT BY THE HOD,

PRINCIPAL/HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF ISOBARIC ROPIVACAINE 0.75% WITH DEXMEDETOMIDINE AND CLONIDINE AS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES** is a bonafide research work done by **Dr. Ashish Tyagi** under the guidance of **DR. JAYSHRI DESAI.**

Dr. HETAL PARIKH

Seal & Signature of the HOD

Date:

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Seal & Signature of the Dean

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DECLARATION BY THE CANDIDATE

I hereby declare that **Sumandeep Vidyapeeth** Pipariya, Vadodara District, Gujarat have the rights to preserve, use and disseminate this dissertation/thesis in print or electronic format for academic/research purpose.

Date: **Signature of the Candidate**

Place: **Dr. Ashish Tyagi**

ACKNOWLEDGEMENTS

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ABSTRACT

Background and Objectives:

Effect of intrathecal dexmedetomidine& clonidine as an adjuvant to isobaric ropivacaine in spinal anesthesia for lower limb & lower abdominal surgeries is not much studied. The objective was to assess the effect of dexmedetomidine 5 mcg & clonidine 30mcg as an adjunct to isobaric ropivacaine in spinal anesthesia.

Materials and Methods:

Sixty selected patients were randomized to receive intrathecal 0.75% isobaric ropivacaine 3ml with clonidine 30mcg & dexmedetomidine 5 mcg in spinal anesthesia for lower limb & lower abdominal surgeries. Block characteristics, hemodynamic changes, postoperative analgesia and adverse effects were compared. **Results:** Both groups were comparable regarding sensory & motor block characteristics and postoperative analgesia.

Conclusion: We conclude that spinal anesthesia with isobaric ropivacaine 3ml with dexmedetomidine 5 mcg is better than clonidine 30mcg.

Keywords: clonidine, dexmedetomidine, isobaric ropivacaine.

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INTRODUCTION

Pain is an unkind sensory and sensitivepractice associated with actual or potential tissue damage. Postoperative pain management holds the key aspect of postoperative care, as acute pain, regardless of its site and suffering, has many other consequences like respiratory depression, adverse circulatory and metabolic stress responses resulting in increased morbidity and mortality. Hence, alleviation of postoperative pain should be a prime goal in anaesthesia.

Postoperative pain relief helps in early patient mobilization, reduction of respiratory complications, good patient's outcome, decreased morbidity and improved patient's satisfaction.[1]

Spinal anaesthesia is a popular modality for lower abdominal and lower limb surgery. It has the benefit of simple procedure, quicker onset of action and dependability in generating generalized sensory and motor blockade. Its demerit is shorter duration and hence devoid of long lasting postoperative analgesia.

To surpass this issue, administration of local anaesthetics in permutation with different adjuvants is a fair method which provides early commencement and prolonged duration of sensory and motor blockade of subarachnoid block and hence acts as synergistic to local anaesthetics with lower local anaesthetic requirement, reduced side effects and excellent postoperative analgesia.

Newer opioids are the popular adjuvants for this purpose.[2,3]Benzodiazepine (midazolam) has also shown promising results in various studies.[4, 5, 6]

Ketamine is also used intrathecally in various studies.[7, 8] However the search for a better adjuvant which provides all the benefits desirable during regional anaesthesia always exist.

Most of the clinical studies about alpha2 receptor agonists are related to the clonidine.

Clonidine, an α-2 adrenergic agonist potentiates local anaesthetics effect and permits reduction in the required doses. Clonidine is a partial α-2 adrenergic agonist used intrathecally with well-established potency and care with effective enhancement of both motor and sensory spinal blockade.[9,10,11,12,13].

Dexmedetomidine, another member of α-2 agonists family, is recently being introduced in India and is approved as an intravenous sedative and co-analgesic drug.

It possesses 10 times higher affinity for α-2 receptors than clonidine.[14]

AIMS AND OBJECTIVES

The following parameters were observed.

1. Onset of sensory and motor block.
2. Duration of sensory and motor block.
3. Duration of analgesia and Rescue Analgesia.
4. Haemodynamic changes like heart rate and blood pressure.
5. Side effects and complications (if any).

REVIEW OF LITERATURE

In 1995 **Y. Harada, L.M. Kitahata, K. Nishioka, K. Kishikawa, J.G. Collins**[23] carried out animal study in rats to demonstrate visceral antinociceptive effect clonidine combined with morphine in spinal and they found that spinal combination of α2 adrenergic and μ- or delta but not k opioid agonists may be beneficial in the control of visceral pain.

In 1998 **H. Buerkle and T.L.Yaksh**[24] did preclinical study in rats to examine whether different α2 adrenergic receptor subtypes differentially mediate antinociception and sedation. They measured the relative potency of three α2 adrenergic agonists, dexmedetomidine, clonidine, and UL-14.304 after spinal and intraventricularly administration. They concluded that α2 adrenergic agonists produce sedation at supra-spinal and spinal sites and these effects are reversed in a dose dependent manner by yohimbine.

In 1999, **Robert D, Eric Evans, Laura A, Renee G.**[28] carried out a study in 30 women in early labor to examine the effect of spinal clonidine administered with spinal sufentanil and bupivacaine on labor analgesia using a combined spinal epidural technique. Patients were received 2 ml spinal injection of sufentanil 7.5μg + bupivacaine 2.5mg with or without clonidine 50 μg. They found that analgesia was significantly prolonged in patients who received spinal sufentanil+ bupivacaine+ clonidine (-2 agonist) (197±70 vs 132± 39; P= 0.004). Side effects, pain score, motor block, sedation and hypotension were similar between two groups.
α

In 2000, **Toshio Ashno, Shuji, Shuichiro, Hiroyuki Shimonaka and Hioki lida**[25] carried out study in spinal cord and brain of rat to examine the analgesic action of three α2 adrenergic agonists when they were given by systemic or epidural injection and found that spinal antinociception caused by the epidural administration of α2 adrenergic agonists is well correlated to their binding affinity to spinal α2 adrenoceptors.

In 2001, **Gyongyi Howawath, Gabriella Joo, Lidiko Dobos, Walter Klimscha,Geza Toth*et al***[26]Carried out study in rat to examine the synergistic effect ofdexmedetomidine, endomorphine-1 and S(+)ketamine after giving it intrathecally and they concluded that there is synergistic effect of above mentioned three drugs when given intrathecally.

In 2002, **I. Dobrydnjov, K. Axelsson, J. Samarutel, B. holmstrom**[29]carried out a study in 45 ASA I and II orthopedic patients scheduled for osteosynthesis of traumatic femur fracture to evaluate the postoperative analgesic and adverse effect of equal doses of oral or intrathecal clonidine. Patients were randomized into 3 groups. One group were received 15 mg bupivacaine only, 2nd received 15 mg bupivacaine+ 150µg clonidine orally and 3rd group received 15 mg bupivacaine+ 150 µg clonidine intrathecally. They concluded that addition of intrathecal clonidine (-2 agonist) prolonged analgesia (236±27min, 313±29min, 337±29min in 1st, 2nd and 3rd group respectively) and decreased morphine consumption postoperatively more than oral clonidine (33.4±2mg, 31.2±3.1mg, , 19.3±1.3mg in 1st, 2nd and 3rd group respectively).

In 2003 **I. Dobrydnjov, K. Axelsson, P. methiesen, H. Klockoff. A Gupta**[30] carried out a study in 45 patients scheduled for inguinal herniorrhaphy to evaluate the postoperative analgesia produced by 15µg and 30µg clonidine added to bupivacaine 6mg intrathecally. They found that group that received 15µg clonidine had significantly higher spread of sensory block than bupivacaine alone. Two segment regression, return of S1 sensation and regression of motor block were significantly prolonged in group which received 30µg clonidine (α2 agonist).

In 2004, **Stephan Strebel, Jurg A. Gurzeler, Markus C. Schneider, Armin Aeschbach and Christoph h. Kindler** [31]carried out a study to in 80 orthopedicpatients posted for hip or knee arthroplasty to examine dose response relationship of intrathecal clonidine with respect to prolonging bupivacaine spinal anaesthesia. They randomized the patients into four groups 1st group were received isobaric 0.5% bupivacaine 18mg+ saline, 2nd group were received bupivacaine +clonidine 37.5µg, 3rd group were received bupivacaine +clonidine 75µg and 4th group were received bupivacaine +clonidine 150 µg. They found that duration of sensory block was increased in patients receiving intrathecal clonidine:(288±62min, 311±101min,325±69min and 337±78min in 1st, 2nd , 3rdand 4th group respectively. They concluded that small dose intrathecal clonidine (α -2 agonist) significantly prolong the anesthetic and analgesic effects of bupivacaine in a dose-dependent manner and that 150 µg of clonidine seems to be the preferred dose, in terms of effect versus untoward side effects, when prolongation of spinal anesthesia is desired.

In 2005, **Katsauki Tanaka, Yutaka Oda, Tomoharu Funao, Ryota Takahashi***etal*[27]studied rats for convulsive potency of bupivacaine and

levobupivacaine end theyfound that dexmedetomidine decreases the convulsive potency of bupivacaine and levobupivacaine.

In 2006 **G. E. KANAZI,M.T.AOUAD,S.I.JABBOUR-KHOURY, Al Jazzar, M.M. Alameddine, R. Al-Yaman *et al*[19]**conducted a study in 60 patients whounderwent transurethral resection of prostate or transurethral resection of bladder tumor under spinal anaesthesia to compare effect of dexmedetomidine and clonidine. They randomized the patients into three groups. 1st group received 12mg hyperbaric bupivacaine, 2nd group received 12mg hyperbaric bupivacaine +3µg dexmedetomidine and 3rd group received 12mg hyperbaric bupivacaine+ 30µg clonidine. They found that mean time of sensory regression to the $S_1$was 190±48min, 303±75min and 272±38min in 1st, 2nd and 3rd group respectively. Time to regression to Bromage scale 0 was 163±47, 250±76 and 216 ±35 in 1st, 2nd and 3rd group respectively.They concluded that dexmedetomidine or clonidine when added to bupivacaine produces a similar prolongation in the duration of the motor and sensory block with preserved haemodynamic stability and lack of sedation.

In 2009, **A. M. Hennaway, A.M. Abd-Elwahab, A. M. Elmaksoud, H. S. El-ozairy and S.R. Boulis[32]**conducted a study in 60 pediatric patients(06 months to 06 years)undergoing lower abdominal surgery to compare the analgesic effect of dexmedetomidine and clonidine in caudal block when added to bupivacaine. They randomized the patients into three groups. 1st group received bupivacaine 0.25% (1 ml/kg)+dexmedetomidine 2µg/kg in 1ml normal saline, 2nd group received bupivacaine 0.25% (1 ml/kg)+ clonidine 2µg/kg in 1ml normal saline and 3rd group received bupivacaine 0.25% (1 ml/kg)+1ml normal saline.They found that addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia

time 16 hours, 12hours and 5 hours with 1st, 2nd and 3rd group respectively. They concluded that addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia in children undergoing lower abdominal surgeries with no significant advantage of dexmedetomidine over clonidine and without an increase in incidence of side effects.

In 2009, **Subhi M. Al-Ghanem, Islam M. massad, Mohamoud M. Al-Mustafa, khaled R. Al-Zaben, Ibrahim Y Qudaisat, Ayman m Qatanweh et al**[3]conducted astudy in 66patients who were having ASA physical status I, II and III scheduled for vaginal hysterectomy, vaginal wall repair and tension free vaginal wall repair to evaluate the onset and duration of sensory and motor block as well as operative analgesia and adverse events of dexmedetomidine or fentanyl given intrathecally with plain 0.5% bupivacaine for spinal anaesthesia. They randomized the patients in two groups. 1st group received isobaric bupivacaine 0.5% 10mg+ 5 µg dexmedetomidine and 2nd group received bupivacaine 0.5% 10mg+ 25mg fentanyl.

They found that mean time for sensory block regression in 1st group was 274 ±73min and in 2nd group was179 ±47min.($p<0.001$). Regression time for motor block to reach modified Bromage scale 0 in 1st group was 240 ±60min and for 2nd was 155 ±46min.They concluded that 10mg isobaric bupivacaine supplemented with 5 µg dexmedetomidine produces prolonged motor and sensory block compared with 25 µg fentanyl.

In 2009, **Ibrahim F. A. Khallifa**[22]conducted a study in 50 ASA Grade I and II patients scheduled for elective inguinal hernia repair under spinal anaesthesia. Purpose of this study was to compare the effect of adding dexmedetomidine or sufentanil to hyperbaric bupivacaine in spinal anaesthesia. They randomly allocated

the patients in two groups, each of 25 patients. 1st group received inj. Bupivacaine 0.5% heavy 2 ml+5 µg dexmedetomidine and 2nd group received inj. Bupivacaine 0.5% heavy 2 ml+ 25 µg sufentanil. They noticed regression time to S_1 dermatome 290 ±55.2 min and 150±42.6min in 1st and 2nd groups respectively. Time to reach Bromage scale 0 was 220±77.3min and 140±86min in 1st and 2nd group respectively.

They didn't find statistically significant difference in terms of cardiovascular stability and complications between two groups.

They concluded that 5µg dexmedetomidine is as good as 25 µg sufentanil when added to the hyperbaric bupivacaine in spinal anaesthesia.

In 2010, **Mausami neogi, Dhurjoti Prosad Bhattacharjee, Satrajit Dawn, Nilay Chatterjee**[33]conducted a study in 75 pediatric patients (1-6 years) undergoingelective inguinal herniotomy to assess and compare the potency of clonidine and dexmedetomidine used as adjuvant to ropivacaine for caudal analgesia in pediatric patients. They divided the patients in 3 groups in randomized fashion. 1st group received 1ml/kg of ropivacaine 0.25%, 2nd group received 1ml/kg 0.25 % ropivacaine and 1µg/kg clonidine and 3nd group received 1ml/kg 0.25 % ropivacaine and 1µg/kg dexmedetomidine. Postoperative analgesia was assessed by CRIES scale. The mean analgesia time was 6.32±0.46hours, 13.17±0.68hours and 15.26±0.86hours in 1st, 2nd and 3rd group respectively. They concluded that addition of clonidine or dexmedetomidine with ropivacaine administered caudally significantly increase the duration of analgesia.

In 2011, **Sukhminder jit singh Bajawa, Sukhwinder Kaur Bajawa, Jasbir Kaur, Gurpreet Kaur, Sachin Gupta, Vikramjeet Arora *et al*[34]**conducted a study in 50patients who underwent vaginal hysterectomy to compare the effect of

dexmedetomidine and clonidine added to ropivacaine in epidural anaesthesia. Patients were randomly allocated in two groups one of which received 17ml of 0.75% ropivacaine+1.5µg/kg of dexmedetomidine and another group received 17ml of 0.75% ropivacaine+2µg/kg of clonidine. They found that 1st group had early onset of analgesia(8.52±2.36min) at T_{10} as compared to 2nd group(9.72±3.44min). Maximum sensory anaesthetic level was obtained earlier (13.14±3.96min) as compared to 2nd group(15.80±4.86min). Modified Bromage scale was achieved earlier in 1st group(17.24±5.16min) as compared to 2nd group (19.52±4.06). They concluded that dexmedetomidine is a better than clonidine in epidural anaesthesia as far as patient comfort, stable cardio-respiratory parameters, intraoperative and postoperative analgesia is concerned. Dexmedetomidine has a superior sedative and anxiolytic properties than clonidine during the surgical procedure under regional anaesthesia.

In 2011 **Rajani Gupta, Jaishi Bogra, Reetu Verma, Monica Kohli, JitendraKumar Kushwaha, Sanjiv Kumar *et al***[20]conducted the study in 60 patientsscheduled for lower limb surgery to evaluate the efficacy and safety of intrathecal dexmedetomidine added to ropivacaine. Patients were randomly allocated into two groups. 1st group received 3ml of 0.75% isobaric ropivacaine+0.5ml normal saline and 2nd group received 3ml of 0.75% isobaric ropivacaine+5 µg dexmedetomidine. They found that mean time for regression sensory block to S_2 was significantly prolonged in 2nd group(468±36.78min) as compared to 1st group (239.33±16.8min). Duration of analgesia was significantly prolonged in 2nd group (478±20.9min) as compared to 1st group (241.67±21.67min). In 2nd group two patients had bradycardia and two patients require ephedrine for hypotension. They concluded that the addition of dexmedetomidine to ropivacaine intrathecally brings prolongation in the duration of motor and the sensory block without any serious adverse event.

In 2011, **Rajani Gupta, Reetu Verma, Jaishi Bogra, Monica Kohli, RajeshRaman, Jitendra Kumar Kushwaha, *et al***[21]conducted the study in 60 patients ofASAI and II posted for lower abdominal surgery to assess the onset and duration of sensory and motor block, hemodynamic effect, postoperative analgesia and adverse effect of dexmedetomidine or fentanyl given intrathecally with hyperbaric 0.5% bupivacaine. Patients were randomly assigned in two groups. 1st group received 12.5 mg hyperbaric bupivacaine+5µg dexmedetomidine and 2nd group received12.5 mg hyperbaric bupivacaine+25µg fentanyl intrathecally. Mean time of sensory regression to $S_1$was 476±23min and 187±12min in 1st and 2nd group respectively. The regression time to reach Bromage scale 0 was 421±21min and 149±18min in 1st and 2nd group respectively. There was rapid onset of sensory as well as motor block. In first group one patient had nausea, three had hypotension requiring ephedrine, one had bradycardia requiring atropine and one had urinary retention. Where in 2nd group two patients had nausea, one had vomiting, two had hypotension and one had urinary retention.They concluded that Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics in 24 hours as compared to fentanyl.

In 2013 , **Vidhi Mahendru, Anurag Tewari, Sunil Katyal, M Rupinder Singh, Anju grewal, Roohi Katyalet al**randomly choose four groups (30 patients each). Group BS received 12.5 mg hyperbaric bupivacaine with normal saline, group BF received 12.5 mg bupivacaine with 25 g fentanyl, group BC received 12.5 mg of bupivacaine supplemented 30 g clonidine, and group BD received 12.5 mg bupivacaine plus 5 g dexmedetomidine. The onset time to reach peak sensory and motor level, the regression time of sensory and motor block, hemodynamic changes. Patients in Group BD had significantly elongated sensory and motor block times than

patients in Groups BC, BF, and BS with Groups BC and BF having similar duration of sensory and motor block. The mean time of two segment sensory block regression was 147 ± 21 min in Group BD, 117 ± 22 in Group BC, 119 ± 23 in Group BF, and 102 ± 17 in Group BS ($P < 0.0001$). The regression time of motor block to reach modified Bromage zero (0) was 275 ± 25, 199 ± 26, 196 ± 27, 161 ± 20 in Group BD, BC, BF, and BS, respectively ($P < 0.0001$). The onset times to reach T8 dermatome and modified Bromage 3 motor block were not significantly different between the groups. Dexmedetomidine group showed significantly less and delayed requirement of rescue analgesic and concluded that Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand of rescue analgesics in 24 h as compared to clonidine, fentanyl, or lone bupivacaine.

In 2016**Swati Srivastava, Urvashi Yadav , Rakesh Verma, Shagufta Naaz and Dheer Singh,etal** randomized 60 patients to 2 groups receiving intrathecal isobaric ropivacaine 18 mg (2.4 ml) combined with normal saline (Group R) or clonidine 30 μg (Group RC); all solutions were diluted with saline to 2.6 ml. We compared block characterstics, hemodynamic changes, post-operative analgesia and adverse effects of both the groups. Results showed that clonidine not only significantly reduced the onset time both of sensory and motor block, but also prolonged the duration. Hypotension and bradycardia was more with clonidine group during first hour. The addition of clonidine prolonged time to first analgesic request and decreased postoperative pain with minimal risk of delayed hypotension. Level of sedation and other side effects were comparable in both groups and concluded that adding clonidine 30 μg to ropivacaine 18 mg produced an early and prolonged spinal anaesthesia and decrease the dose of post-operative analgesic requirement.

ANATOMY OF SUBARACHNOID SPACE

The vertebral column is made up of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumber, 5sacral (fused) and 4 coccygeal.

Spinal canal runs from foramen magnum to sacral hiatus.

A typical vertebra is composed of following parts: [35]

BODY:

Which is weight bearing and separated from adjoining vertebral bodies by the intervertebral disc.

THE VERTEBRAL ARCH:

It is composed of pedicles and lamina which surround and protect the spinal cord and its coverings.

THE TRANSVERSE AND SPINOUS PROCESS:

It gives attachment to ligaments and muscle acting on the vertebral column.

SUPERIO AND INFERIOR ARTICULAR PROCESS:

Each pedicle is grooved, especially on lower surface. These grooves are termed superior and inferior vertebral notches and together make up the intervertebral foramen for the passage of spinal nerves. The transverse process arises at the junction of pedicle and lamina. The lumbar vertebrae, five in numbers, have large and massive kidney shaped bodies because of their weight

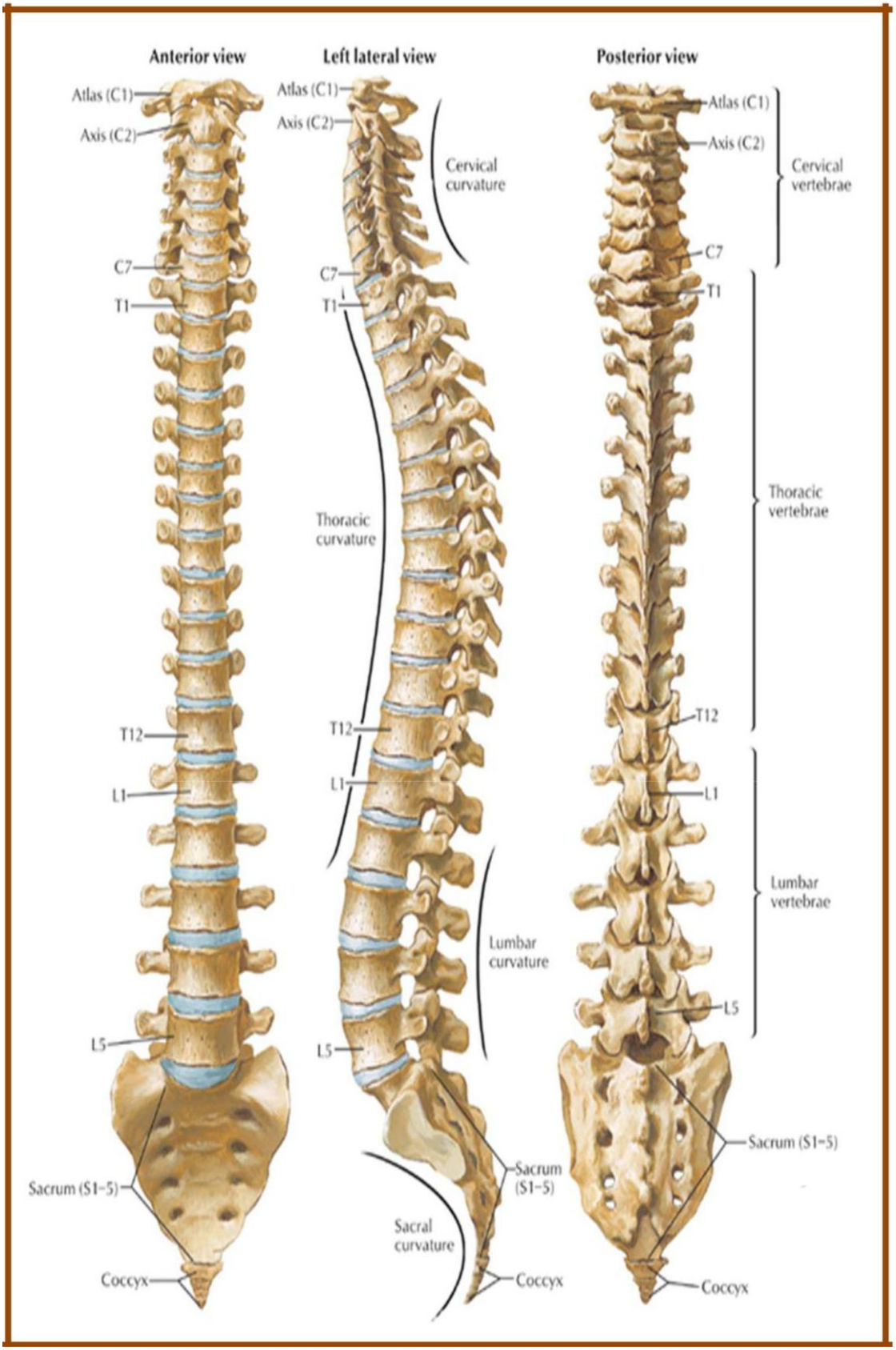

Figure 1: Anatomy of vertebral column

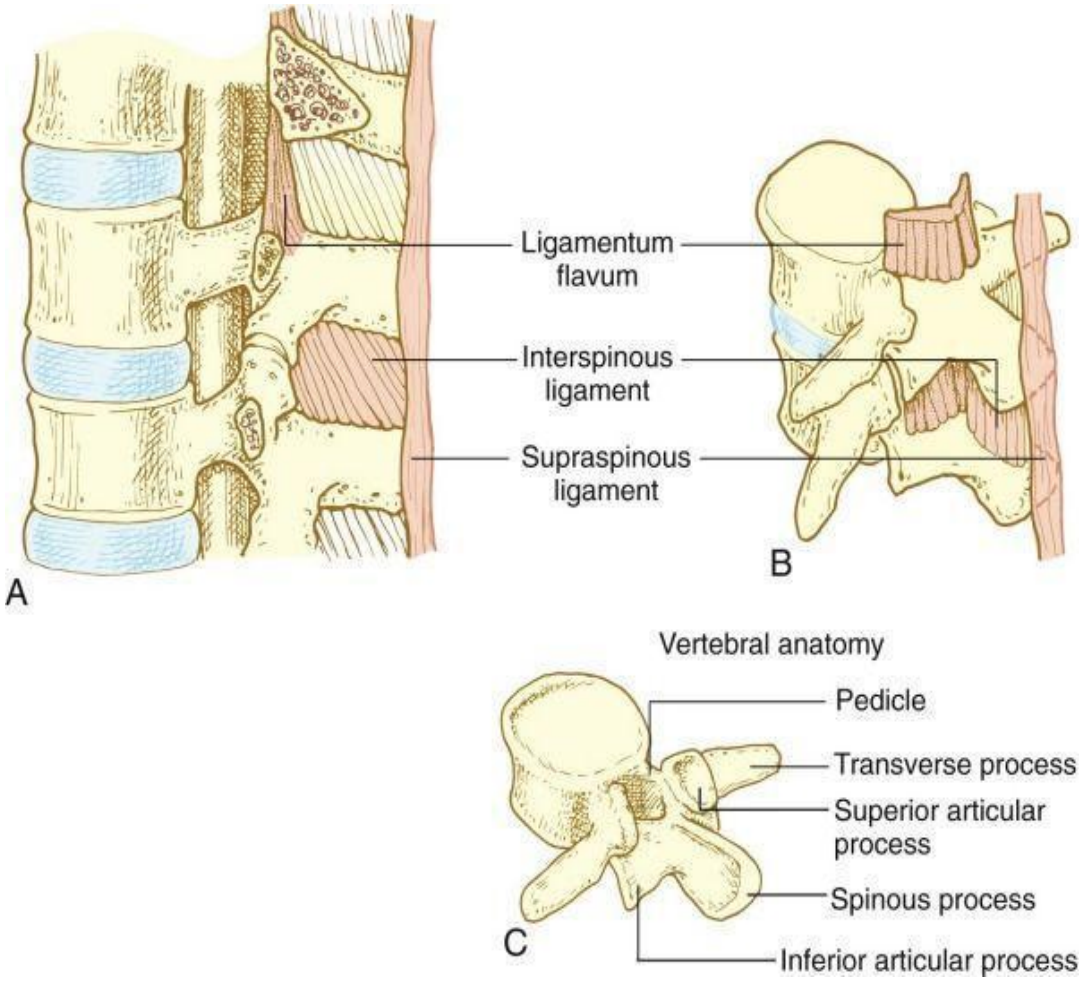

Figure 2 : Anatomy of vertebra.[36]

The superior intervertebral notch is small and inferior is large. The laminae are thick and sloping and spinal canal is triangular. The spine is hatch shaped and projects backward nearly horizontally.

The vertebral arches of neighbouring vertebrae are bound together by three ligaments which are of interest to anesthesiologists.

LIGAMENTUM FLAVUM: [37]

It is composed of entirely of yellow elastic fibers. It runs from anterior and inferior aspect of laminae above and superior aspect of laminae below. Laterally it blends with the capsule of facet joint and medially with the interspinous ligament or with its fellow of the opposite side.The ligament is thinnest at cervical region and thickest in the lumbar region where powerful stress and strain has to be encountered.

INTERSPINOUS LIGAMENT: [37]

It connects adjoining spinous process from their tips to their roots. They fuse with the supraspinous ligaments posteriorly and with the ligament flavum anteriorly. In the lumbar region they are wide and dense.

THE SUPRASPINOUS LIGMENT: [37]

It unites the tips of spinous process from the seventh cervical vertebrae to sacrum. It is thickest and widest in the lumbar region. The anterior and posterior longitudinal ligaments bind the bodies of the vertebrae in front and behind, running from axis to sacrum.

The intervertebral discs are responsible for a quarter of the length of spinal column and functionally are shock absorbers placed between the vertebral bodies. Each disc consists of peripheral fibrous portion -the annulus fibrosus and a gelatinous central part -the nucleus pulposus**.**

SPINAL CORD:

It is a direct continuation of the medulla oblongata. It begins at the upper border of the atlas and ends in the adults usually at the lower margin of the first lumbar vertebra being 42.5 cm in length. From the lower end of this extends a thread like structure known as filum terminale interna which ends with the dura and arachnoid mater at the level of 2nd sacral vertebrae. [35]

BLOOD SUPLY OF THE SPINAL CORD: [37]

1. Anterior spinal artery.
2. Posterior spinal artery.

The spinal arterial supply by the above two arteries is reinforced by many spinal radicular branches arising from local segmental arteries, like vertebral, cervical radicular, thoracic radicular and most important being artery of Adamkiewicz. (figure.3)

Spinal veins drain through intervertebral foramen into vertebral, azygous and lumbar veins.

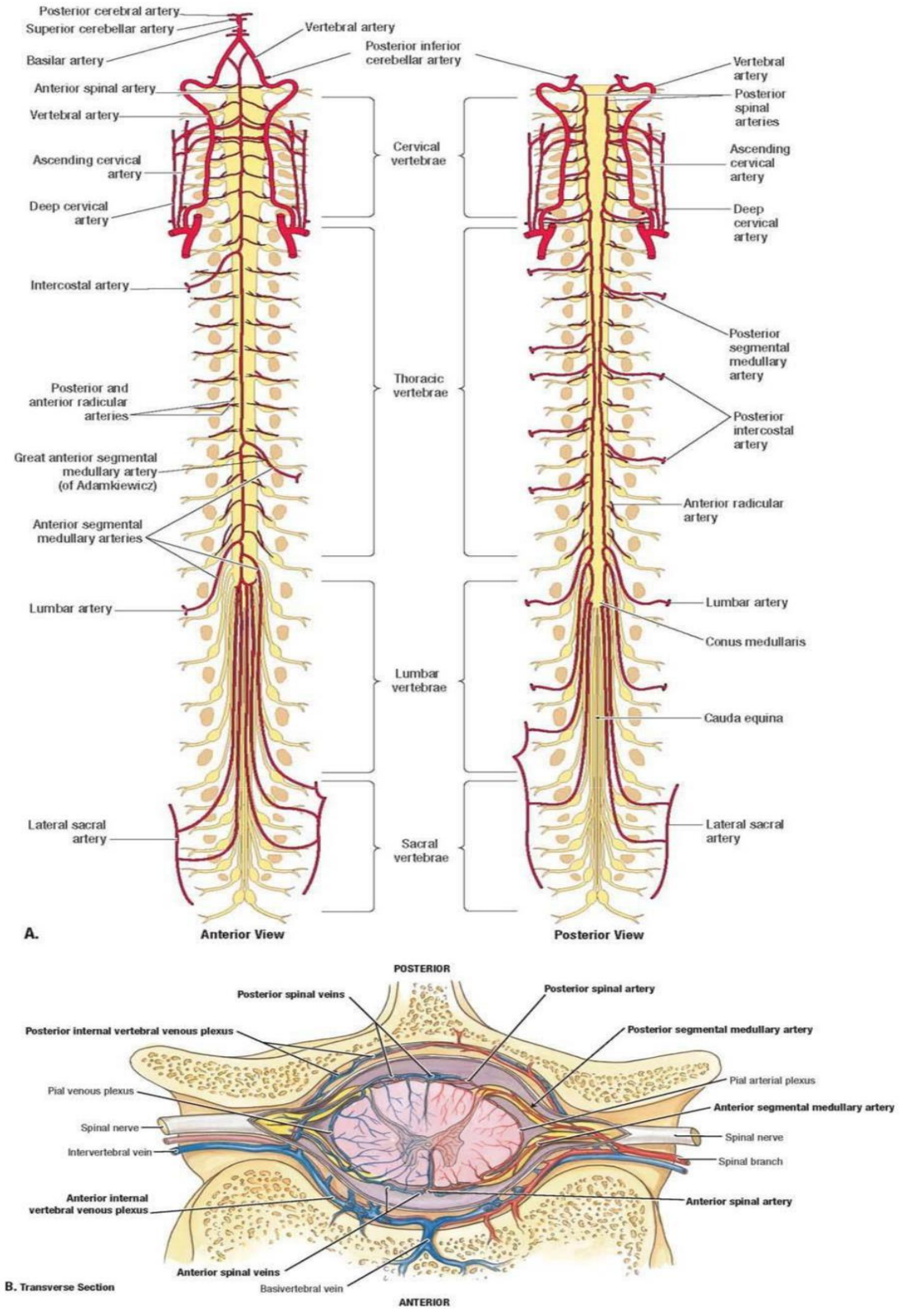

Figure 3: Blood Supply of spinal cord

MENINGES: [35]

The spinal cord is enveloped by three membranes Dura, Arachnoid and Pia mater, which are direct continuation of those surrounding the brain (figure5).

In the cranial cavity the dura is arranged in two layers, endosteal and meningeal, which are firmly adherent except where they split to enclose venous sinuses. The outer endosteal layer is the periosteum of the inner surface of the skull bones and in the spine, acts as the periosteum lining the spinal canal. The inner layer is continued from the cranium into the spinal canal but is firmly adherent to margin of the foraman magnum where it blends with the outer endosteal layer. Between the spinal dura and the periosteum lining the spinal canal is the epidural space.The dura and subarachnoid end as a tube usually at the 2nd sacral vertebrae, so spinal cord is not found below this level.

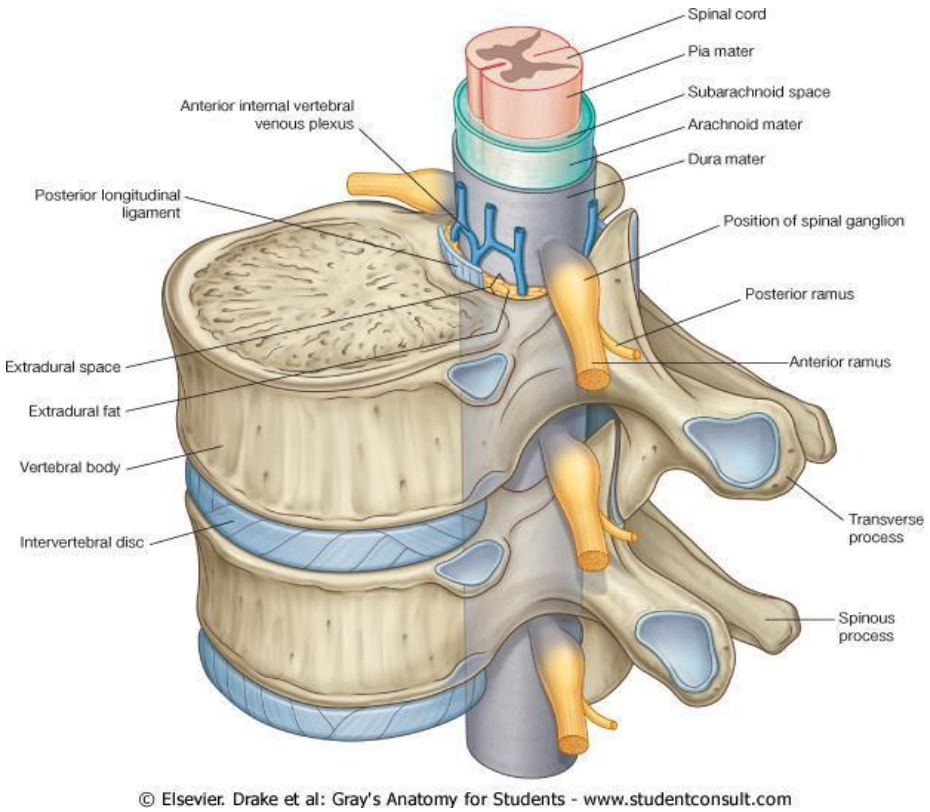

Figure 4 : Meningeal layers of spinal cord. [35]

In the vertebral canal, the pia is closely applied to the spinal cord and extends into the anterior median fissure. The arachnoid mater is the middle of the three investing membranes covering the brain and spinal cord and is closely applied to the dura mater. The subarachnoid space contains the cerebrospinal fluid and is divided by an incomplete midline septum along the dorsal surface of the cord. The subdural space between the dura and the arachnoid is a capillary interface containing a little serous fluid.

SUBARACHNOID SPACE:

It is lined externally by the arachnoid mater and internally by the pia mater and innumerable cobweb like trabeculae run between the two membranes. It is traversed by cranial and spinal nerves. It houses the main vessels of cranial nervous system and cerebrospinal fluid. Spinal cord finishes at lower border of L1 vertebrae and subarachnoid space below this level is circular and has a diameter of 15 mm. Thus lumbar puncture should be carried out in the lower lumbar region.

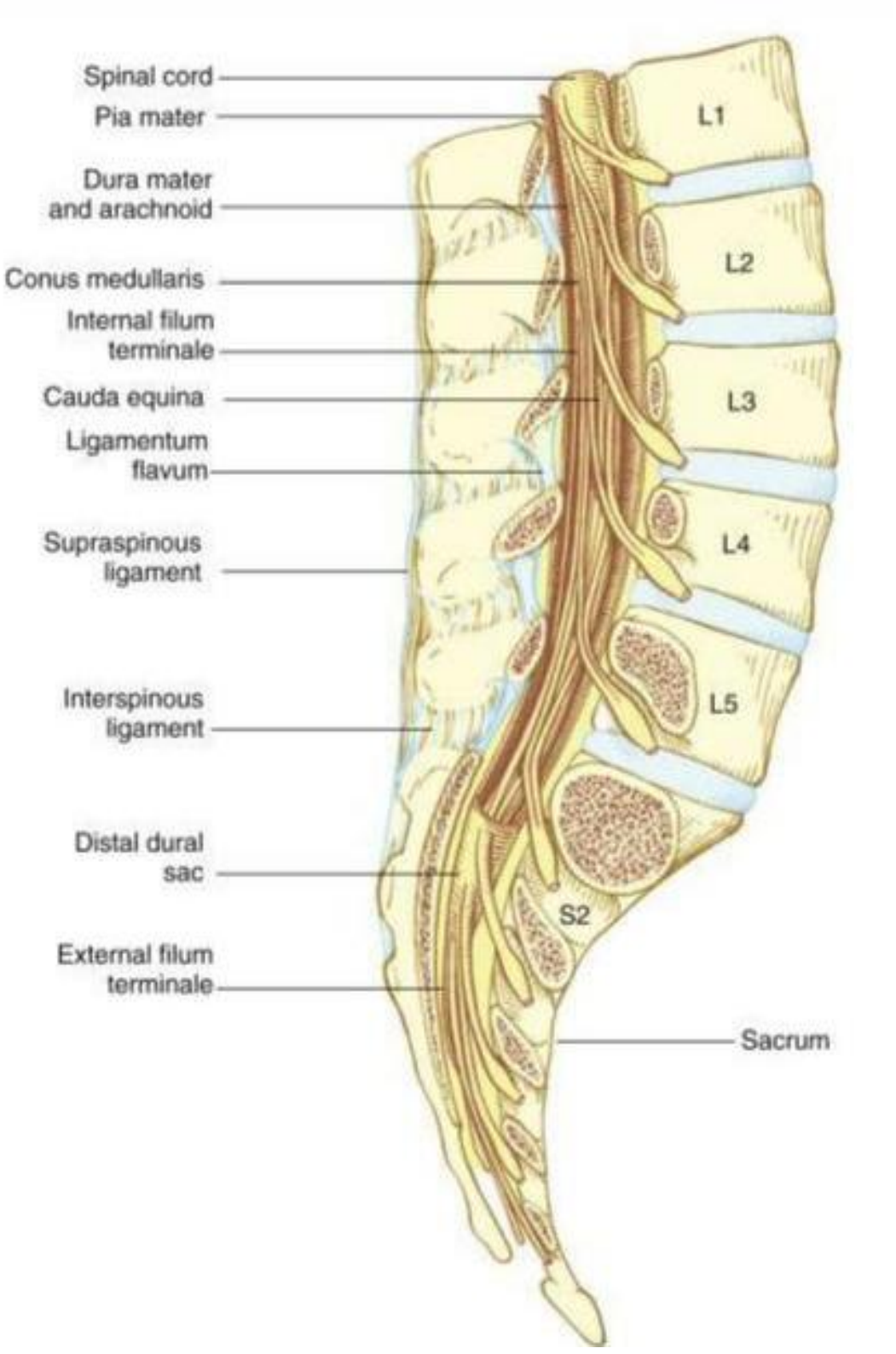

Figure: 5 Subarachnoid and Epidural space

PHYSIOLOGY OF CEREBROSPINAL FLUID

CEREBROSPINAL FLUID:

The term CSF was first used in 1825 by French physiologist Magendie. It is a clear, colorless fluid, slightly opalescent due to globulin present in cerebral ventricles and subarachnoid space. It is produced by choroid plexus of lateral, third and fourth ventricles by either secretion or ultra-filtration at a rate of 0.4 ml/minute.

PHYSICAL CHARACTERISTICS:

Volume: 100 to 150 ml (8% of intracranial content)

Distribution: 35 ml in ventricles, 25 ml in cerebral subarachnoid space and75 ml in spinal subarachnoid space.

Pressure: 70 -180 mm of water in lateral position

350-550 mm of water in sitting position

Specific gravity: 1.004-1.009

Drainage: Into venous sinuses of brain via the arachnoid villi and into thelymph stream via the pacchionion bodies.

Cells: Poor in cells, only 4-5 lymphocytes/ml.

CHEMICAL COMPOSITION (Human CSF) :

pH	:	7.4
proteins	:	20-40%

Glucose	:	45-80 mg%
Urea	:	10-30 mg%
Ca^{+2}	:	2.3 mEq/L
Na^{+}	:	135-147 mEq/L
K^{+}	:	2.9 mEq/L
Cl^{-}	:	115-135 mEq/L
HCO3-	:	25mEq/L
Pco_2	:	50 mmHg
Lactic acid	:	18.0 mg%
Osmolality	:	298 mOsm/kg H_2O

FUNCTIONS:

1. It acts as a hydraulic shock absorber protecting the brain and the spinal cord.
2. By its absorption and formation it can accommodate changes in volume of other cranial contents.
3. It removes the waste product of cerebral cellular metabolism.
4. It provides nutrition.
5. It regulates pulmonary ventilation by its pH changes.

PHYSIOLOGY OF PAIN

What is pain?

The International Association for Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[39] "It is to be noted that pain is not just a physical sensation. It is also an emotional experience. It differs from person to person and in the same person from time to time. There may be a strong emotional component contributing to the pain experience; but that does not mean that the suffering is less important. A simple definition of pain is "Pain is what the patient says, hurts."[40]The emphasis is on the patient's experience."

Pain is a defensive mechanism of the body, it occurs whenever any tissue is being damaged, and it causes the individuals to react, to remove the painful stimulus. It also helps in diagnosis of underlying tissue damage.

Nociception: It is a neural response to painful and harmful stimuli. All nociceptionproduces pain, but all pain may not result into nociception.

CLASSIFICATION OF PAIN:

(A) FAST PAIN AND SLOW PAIN:

Fast Pain:

It is transmitted through type A pain fibers which are 2-5 microns in diameter, fine myelinated and relatively rapidly conducting (12-30 m/sec). It occurs within 0.1

second of application of localized painful stimulus like pin prick, skin cut by knife. It is felt in most of the superficial tissues of the body.

Slow Pain:

It is transmitted through type C unmyelinated fibers which are 0.4-1.2 micron in diameter and conducting at rate of 0.5-2 m/sec. It begins only after a second or more and then increases slowly over a period of seconds and minutes. It is also called throbbing, burning, aching, and chronic pain. This type of pain is usually associated with tissue destruction. It can occur in both skin and deeper tissue of the body.

(B) ACUTE PAIN AND CHRONIC PAIN:

Acute Pain:

It is primarily due to nociception due to injury, abnormal function of viscera and a disease process. Most common form: post- operative, post traumatic, obstetric and pain associated with myocardial infarction, pancreatitis, and renal calculus. It is sometimesself-limiting or resolves in few days to weeks with treatment of underlying pathology, when fails to resolve it becomes chronic.

Somatic Pain:

- Superficial / Cutaneous pain: It is well localised and sharp pricking, throbbing and of burning quality.
- Deep pain: pain impulse from ligaments, tendons, joints, muscle and fascia arise in a network of fine fibers similar to those in the skin and travel by the same nervous pathways, but the segmental innervation of these structures does not

necessarily correspond with that of underlying skin. It is dull aching and less well localized.

Visceral Pain:

Due to disease process or abnormal function of an internal organ or its covering. It is always non localized diffuse deep pain. It is associated with either abnormal sympathetic or parasympathetic activity causing nausea, vomiting, changes in blood pressure and heart rate.

Referred Pain:

Deep pain, whether visceral or somatic in origin, may be felt in some part of the body other than the site of stimulation .e.g. reference of cardiac pain to the left arm (inner side) and diaphragmatic pain to shoulder.

Chronic Pain:

Pain which persists beyond the usual course of an acute disease or after a reasonable time for healing to occur varies between 1 to 6 months. May be nociceptive, neuropathic or both.

(C) NEUROPATHIC PAIN:

If pain is **not** caused by a stimulus applied to the nociceptor, but is causedby impulse generation within the pathway proximal to thenociceptor (this could be in the nerve, the spinal cord orthe brain), it is called **neuropathic** pain.

Neuropathic pain can be of three sub-types:

i) Neural injury pain

ii) Nerve compression pain

iii) Complex Regional Pain Syndrome (CRPS)

Neural injury pain can be said to involve anatomical abnormality in peripheralnerves, in pain receptors or in the central pain pathway. The following three features help to diagnose a neuropathic pain.

1. The nature of the pain may be shooting, stabbing, pricking, aching or burning.
2. It has a neural or dermatomal distribution.
3. It is often associated with abnormal sensation in the area of pain.

This can take the form of hypoaesthesia or hyperaesthesia. Unfortunately it often takes the form of dysaesthesia, that is, an unpleasant abnormal sensation either spontaneous or evoked. Hyperalgesia is increased response to a stimulus, particularly a repetitive stimulus, as well as an increased threshold (an exaggerated response with an increase in pain threshold).

Nerve compression pain occurs when there is extrinsic compression on the neuralstructure, as for example with a nerve root compression in prolapsed inter-vertebral disc or with collapsed vertebrae from metastatic lesions.

Neuropathic pain can also be sub-classified into peripheral and central, depending on site of origin of abnormal impulse. The relevance is that central pain often behaves differently from peripheral neuropathic pain, particularly in their response to drugs. Central neuropathic pain is commonest in injury to the CNS – for e.g. spinal cord injuries, stroke etc. It must be remembered that pain originally of peripheral nerve origin, can become centrally established – by somehow altering the CNS. Once this

has happened, a peripheral nerve block or neurolysis may not successfully remove the pain.

Neuropathic pain is less responsive to opioids but responds to local anaesthetics, anticonvulsants and tricyclic antidepressant.

Complex regional pain syndrome (CRPS) is a chronic progressive diseasecharacterized by severe pain, swelling and changes in the skin. The InternationalAssociation for the Study of Pain has divided CRPS into two types based on the presence of nerve lesion following the injury.

- Type I, known as **reflex sympathetic dystrophy** (RSD), Sudeck's atrophy, reflex neurovascular dystrophy (RND) or algoneurodystrophy does not have demonstrable nerve lesions.
- Type II, also known as **causalgia**, has evidence of obvious nerve damage.

The cause of this syndrome is currently unknown. Precipitating factors include injury and surgery, although there are documented cases that have no demonstrable injury to the original site.

Allodynia:

The stimuli that normally are not painful e.g., movement and light touch become painful. The pain produced by touching burnt skin or movement of an arthritic joint.

PAIN RECEPTOR AND THEIR STIMULATION:

All pain receptors in the skin and peripheral tissues are free nerve endings. They are widely distributed in the superficial layers of the skin as well as in the arterial walls, periosteum, joint surfaces and falx and tentorium cerebri of the cranial cavity.Pain

can be elicited by multiple types of stimuli. They are classified as mechanical, thermal and chemical pain receptors. In general, fast pain is elicited by the mechanical and thermal types of stimuli, whereas slow pain can be elicited by all three types.

Some of the chemicals that excite the chemical type of pain include bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine and proteolytic enzymes. In addition, prostaglandins and substance P enhances the sensitivity of pain endings but do not directly excite them. The chemical substances are especially important in stimulating the slow, suffering type of pain that occurs after tissue injury.

PAIN PATHWAY

FIRST ORDER NEURONS

There are two separate pathways for transmitting pain signals into the central nervous system. They are a fast-sharp pain pathway and a slow chronic-pain pathway. The Fast-sharp pain signals are elicited by either mechanical or thermal pain stimuli; they are transmitted in the peripheral nerves to the spinal cord by small A-δ fibres.

The slow-chronic type of pain is superficially elicited by the chemical types of pain stimuli but also at times by persisting mechanical or thermal stimuli; this slow-chronic pain is transmitted by the type C fibres.Because of this double system of pain innervations, a sudden onset of painful stimulus often gives a „double“ pain sensation: a fast-sharp pain that is transmitted to the brain by the A-δ fibre pathway followed a second or so later by a slow pain that is transmitted by the C fibre system. The sharp pain apprises the person rapidly of a damaging influence and therefore plays an important role in making the person react immediately to remove himself

from the stimulus. While slow pain tends to become more and more painful over a period of time.

On entering the spinal cord, afferent fibers ascend or descend one to three segments in the tract of Lissauer that lies immediately posterior to the dorsal horn of the cord gray matter. From the dorsal spinal roots, the pain fibres terminate on neurons in the dorsal horns.

SECOND ORDER NEURONS

On entering the spinal cord, the pain signals take two pathways to the brain through:

1. Neospinothalamic tract.[41]
2. Paleospinothalamic tract. [41]

NEOSPINOTHALAMIC TRACT:

The fast type A-δ pain fibres imparts mainly mechanical and acute thermal pain. They terminate mainly in lamina I (Lamina marginalis) of the dorsal horns and they excite second order neurons of the neospinothalamic tract. These give rise to long fibres that cross immediately to the opposite side of the cord through the anterior commissure and then pass upward to the brain in the anterolateral columns.

The fast-sharp type of pain can be localized much more exactly in the different parts of the body than can slow-chronic pain. However, even fast pain, when only pain receptors are stimulated without simultaneously stimulating tactile receptors, is still quite poorly localized. It is considered truthfully that glutamate is the neurotransmitter substance secreted in the spinal cord at the A-δ pain fibres.

PALEOSPINOTHALAMIC TRACT:

The Paleospinothalamic tract is a much older system and transmits pain mainly carried in the peripheral slow-chronic type C pain fibres; although it does imparts some signals from type A-δ fibres as well. In this pathway, the peripheral fibres terminate almost entirely in the laminas II and III of the dorsal horns, which together are called the substantia gelatinosa. Most of the signals then pass through one or more additional short fibre neurons within the dorsal horns themselves before entering lamina V through VIII, also in the dorsal horn. Here the last neuron in the series gives rise to long axons that mostly join fibres from the fast pathway, passing first through the anterior commissure to the opposite side of the cord and then pointed towards the brain in the same anterolateral pathway.

Type C fibres terminals entering the spinal cord secrete both glutamate transmitter and substance P transmitter. The glutamate transmitter acts instantaneously and lasts for only a few milliseconds. On the other hand, substance P is released much more slowly, building up in concentration over a period of seconds or even minutes.

THIRD ORDER NEURONS:

The slow-chronic type of Paleospinothalamic pathway terminates widely in the brain stem. Only one-tenth to one-fourth of the fibers passes all the way to thalamus. Instead they terminate principally in one of the three areas: (1) The reticular nuclei of the medulla, pons, and mesencephalon; (2) The tectal area of the mesencephalon deep to the superior and inferior colliculi; or (3) The peri aqueductal gray region surrounding the aqueduct of Sylvius. These lower regions of the brain appear to be important in the appreciation of suffering types of pain.

From the brain stem areas, multiple short-fibre neurons relay the pain signals upward into the intralaminar and central lateral nuclei of the thalamus and into certain portions of the hypothalamus and other adjacent regions of the basal brain.

Localization of pain transmitted in the paleospinothalamic pathway is poor. Slow-chronic type of pain can usually be localized only to a major part of the body such as to one arm or leg. It explains why patients often have serious difficulty in localizing the source of some chronic types of pain.

A few fibres of the neospinothalamic tract terminate in the reticular areas of the brain stem, but most pass all the way to the thalamus, terminating in the ventrobasal complex along with dorsal column-medial lemniscal tract for tactile sensation. A few also terminate in the posterior nuclear group of the thalamus. From these areas, the signals are transmitted to other basal areas of the brain and to the somatic sensory cortex.

MODULATION OF NOCICEPTIVE INPUT:

Whenever there is a synapse, there is a possibility of facilitation or inhibition of pain. The spinoreticular tract plays an important role in pain modulation as do the interneurons of the dorsal horn of spinal cord.

a) Facilitation of pain:

- Occurs due to wind up of wide dynamic range fibres in the dorsal horn.It iscaused by NMDA receptor activation on one and on the other hand A-β sensitization mediated via inhibition of pathways that use GABA.
- Expansion of receptive field: The more intense the painful stimulus, the greater the number of activated C fibre afferents. Therefore, intense

stimulation leads to activation of dorsal horn neurons beyond the spinal segment containing the nociceptive source and the receptive field expands. The C fibre input activates several synapses in the dorsal horn with the result that even a small injury produces diffuse pain.

- Cortical factors are involved when a pain is facilitated by anxiety, stress or depression and pain is often perceived to be worse when other afferent inputs are reduced. Pain facilitation may be due, either to the recruitment of pathways or the inhibition of normal inhibitory mechanism.

b) Inhibition of pain:

The pain suppression system of the body has three major components:

(1) The peri aqueductal gray and periventricular areas of mesencephalon and upper pons surrounding the aqueduct of Sylvius and adjacent to portions of the third and fourth ventricles. Neurons from these areas send their signals to (2) the raphe magnus nucleus, a thin midline nucleus located in the lower pons and upper medulla, and the nucleus reticularis paragigantocellullaris located laterally in the medulla. From these nuclei, the signals are transmitted down the dorsolateral columns in the spinal cord to

(2) A pain inhibitory complex located in the dorsal horns of the spinal cord. At this point, analgesic signals can block pain before it is relayed to the brain.

NEUROTRANSMITTERS OF PAIN:

Encephalin: These pentapeptides are secreted by the terminals of short axoninterneurons of CNS. They prevent release of substance P which is responsible for pain. These are rapidly destroyed. It is suggested that patients with lower endorphin levels will require more analgesic drug to obtain acceptable pain relief. Increase in plasma encephalin levels are found after surgery.

Serotonin: Descending serotoninergic neurons from the medulla are believed to beinvolved in pain inhibition. Experimental studies have shown that injection of serotonin increase analgesia of morphine.

Prostaglandins: In the periphery, prostaglandins of the E and I series sensitize painreceptors & PGE‟ s are believed to be involved in the amplification of pain in the inflammatory process. Several others such as Bradykinin, Acetylcholine & Histamine are known to produce intense pain on local injection & may also be involved in the mediation of natural pain.

Substance P: It is found in 10–20 % of small diameter nociceptive sensory neurons.It is located in the synaptic vesicles in the marginal layers & substantia gelatinosa of the dorsal horn of the spinal cord. It would appear to be a neurotransmitter for nociceptive afferents. It is a peptide neurotransmitter.

GABA: Its role is not clear. It has been suggested that central excitatory effects of opioids may be due the inhibition of GABA.

Many of the nerve fibres derived from both periventricular nuclei and peri aqueductal gray area secrete encephalin at their nerve endings. The endings of many of the fibres in the raphe magnus nucleus release encephalin. The fibres generating in the nucleus

but terminating in the dorsal horns of the spinal cord secrete serotonin at their endings. The serotonin in turn causes local cord neurons to secrete encephalin. Encephalin is then known to cause presynaptic inhibition and postsynaptic inhibition of both incoming type C and type A-δ pain fibres where they synapse in the dorsal horns. Because it is calcium ions that cause release of transmitter at the synapse, calcium blockage would result in presynaptic inhibition.

Thus the analgesia system can block pain signals at the entry point to the spinal cord. It can also block many of the local cord reflexes that result from pain signals, especially the withdrawal reflexes.

GATE CONTROL THEORY OF PAIN:

The **gate control theory of pain**, put forward by Ronald Melzack[42](a Canadian psychologist) and Patrick David Wall[43] (a British physician) in 1962 and again in 1965 is the idea that the perception of physical pain is not a direct result of activation of nociceptors, but is modulated by interaction between different neurons, both pain-transmitting and non-pain-transmitting. The theory says that activation of nerves that do not transmit pain signals can interfere with signals from pain fibers and inhibit an individual's perception of pain.

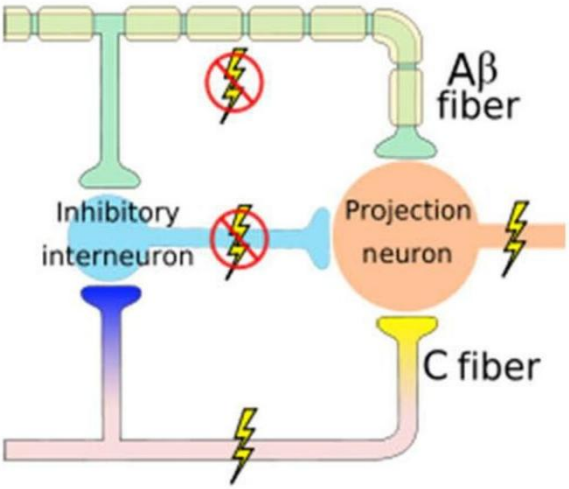

Figure: 6 Pain pathways

The firing of the projection neuron determines pain. The inhibitory interneuron decreases the chances that the projection neuron will fire.

- Firing of the C fibers inhibits the inhibitory interneuron (indirectly), increasing the chances that the projection neuron will fire. Inhibition is represented in blue and excitation in yellow.
- A lightning bolt signifies increased neuron activation, while a crossed-out bolt signifies weakened or reduced activation.

POST OPERATIVE PAIN

PHYSIOLOGICAL EFFECTS OF POST-OPERATIVE PAIN

(1) RESPIRATORY SYTEM:

Pain associated with thoracic and upper abdominal surgery can cause significant postoperative respiratory dysfunction. Pain causes an increase in muscle tone around the site of injury. This “muscle splinting” coupled with voluntary reductions in respiratory muscle excursions, causes reduction in

lung volumes (tidal volume, vital capacity and functional residual capacity and forced expiratory volume in 1 second- FEV_1), regional lung collapse (atelectasis) and reduced alveolar ventilation all of which ultimately result in hypoxemia and hypercapnia. Increased muscle tone is also associated with increased oxygen consumption and lactic acid production. These respiratory changes also result in a reduced ability to cough, retention of secretions and increased risk of chest infections. Adequate perioperative pain relief, coupled with breathing exercises, can reverse these adverse respiratory effects.

(2) CARDIOVASCULAR SYSTEM:

Pain causes reflex stimulation of sympathetic nervous system which results in tachycardia, increased cardiac output, myocardial work load and oxygen consumption. In susceptible individual risk of myocardial ischemia or infarction increases.

(3) GASTROINTESTINAL SYSTEM:

Raised sympathetic activity associated with pain also results in decreased gastrointestinal motility (gastric stasis and paralytic ileus), increased intestinal secretions and increased smooth muscle sphincter tone. Nociceptive impulses from viscera and somatic structure can cause nausea and vomiting.

(4) GENITOURINARY SYSTEM:

Pain causes increases motility of urethra and bladder and consequently causes difficulty in micturition and retention of urine.

(5) NEUROENDOCRINE SYSTEM AND METABOLISM:

Supraspinal reflex response to pain result in increased sympathetic tone and hypothalamic stimulation causing increased release of catecholamines and catabolic hormones like cortisol, ACTH, ADH, GH, C-AMP, glucagon, aldosterone, renin angiotensin-II, and decreased release of anabolic hormones like insulin and testosterone. These responses collectively result in retention of Na+ and water, increased fatty acids, ketone bodies and lactate. Metabolism and oxygen consumption increases. A catabolic state and negative nitrogen balance results if the process continues.

(6) PSYCHOLOGICAL :

Acute postoperative pain leads to fear and anxiety in hospitalised patients. If left unattended, it can progress to anger, resentment and animosity towards medical personnel who may be perceived as withholding pain relief. Sleep deprivation may aggravate these feelings. Patients may go into depression and a feeling of helplessness. Adequate attention to pain relief can help in advancing a feeling of well being which has a positive influence on postoperative outcome.

(7) THROMBOEMBOLIC PHENOMENA:

When fear of aggravating pain results in reduced physical activity, venous stasis and platelet aggregation increases the risk of deep vein thrombosis, pulmonary embolism and cerebrovascular accidents.

ADVANTAGES OF POST OPERATIVE ANALGESIA:

1. Decreased incidence of respiratory complications.
2. Decreased incidence of cardiovascular complications.
3. Early return of gastrointestinal tract function.
4. Early ambulation and early discharge from hospital.

METHODS OF POST-OPERATIVE PAIN RELIEF:

1. Non-Pharmacological:

a) Supportive therapy: Encouragement, reassurance & frequent supportive visits.

b) Psychological: Enthusiastic personal preparation is of the greatest importance & has marked beneficial effect on post-operative progress. The following methods are used:

- Hypnosis
- audio control
- Bio feedback mechanism

c) Acupuncture

d) Mechanical vibratory stimulator.

e) Electrical nerve stimulation: Transcutaneous or percutaneous.

f) Cryoanalgesia.

g) Multiple intramuscular stimulation.

2. Pharmacological:

a) Oral: NSAIDs, Opiates.

b) Rectal suppositories: NSAIDs

c) Intramuscular/Intravenous: Opiates, sub anaesthetic doses of ketamine (0.44mg/kg), NSAIDs.

d) Transdermal: NSAIDs, opiates

e) Surface analgesia: EMLA cream.

f) Extradural (Epidural): Opiates, local anaesthetics & ketamine.

g) Intrathecal: Opiates.

h) Inhalation of analgesic gases: N2O + O2, Trilene + O2, Methoxyflurane + O2

i) Regional nerve blockade: Using local anaesthetic agents.

METHODS FOR ASSESSMENT OF POST-OPERATIVE PAIN:

1. SUBJECTIVE METHODS:

a. The patient is asked to assess the severity of pain.

(1) Verbal response scale: Usually a 4 point VRS is used by simplequestionnaire:

- No Pain

- Mild pain
- Moderate pain
- Severe pain

(2) Non- Verbal response scale: Linear or visual analogue scale is used.

A 10cm line with one end is labelled as "no pain" & other "worst possible pain".

(3) Scoring of pain intensity: Patient assess pain severity on a scale 1, 2, 3,4, 5, 6, 7, 8, 9, & 10. 1 is no pain & 10 is very severe pain.

4. Magill's grading of pain:

- 0 - Patient in sound sleep & on questioning says that he does not feel any pain.
- 1 - On questioning complains of mild bearable pain, but does not require analgesic.
- 2 - Complains of pain & also requests to have some analgesic only on questioning (Moderate pain)
- 3 - Spontaneously complains of pain & requires analgesic (severe pain)

5. Magill's pain questionnaire:

- Assess 20 features of pain using 105 descriptors
- Sensory, affective, evaluative component.
- Provides data on qualitative differences in pain & pain relief method
- Disadvantage: Too long, patient becomes frustrated, in English, rarely used for acute pain.

6. Present pain intensity:

Measured numerically as,

1) Mild pain 2) Discomfort 3) Distress

4) Horrible 5) Excruciating pain.

7. Categorical scale (completed by patient):

1. No pain
2. Just noticeable
3. Weak
4. Mild.
5. Moderate
6. Strong
7. Severe
8. Excruciating

The consumption of systemic analgesic administered to the patient is measured.

Demands for analgesia:

- Time to first demand
- Total dosage of analgesic required in a given time or in 24 hours.
- Frequency of demand.

2. OBJECTIVE METHODS:

i. Observer VRS: Observer assesses the severity of pain by the patient's ability to move, sit or walk without pain.

ii. Measurement of respiratory function like vital capacity, FEV1, PEFR etc.

3. COMBINATION OF SUBJECTIVE & OBJECTIVE METHODS.

4. OTHER METHODS:

a) Recording of evoked electrical potential.

b) Formulation of pain ratio.

PHARMACOLOGY OF DRUGS

ROPIVACAINE

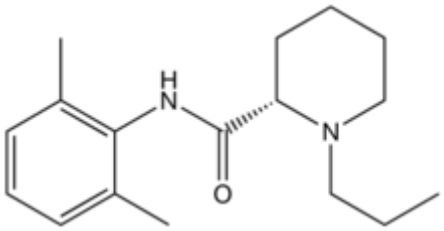

Figure 7: Ropivacaine Structure

Introduction

One of the most important properties of a long-acting local anaesthetic is to reversibly inhibit the nerve impulses, thus causing a prolonged sensory or motor blockade appropriate for anaesthesia in different types of surgeries. [25] The acute pain relief obtained at lower doses in postoperative and labour patients due to sensory blockade is sometimes marred by accompanying motor blockade, which serves no purpose and is quite undesirable.

Bupivacaine is a well-established long-acting regional anaesthetic, which like all amide anaesthetics has been associated with cardiotoxicity when used in high concentration or when accidentally administered intravascularly. Ropivacaine is a long-acting regional anaesthetic that is structurally related to bupivacaine. It is a pure S(-)enantiomer, unlike bupivacaine, which is a racemate, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles.[25]

Physical Properties

IUPAC name-

(S)-N-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamid

Pka	8.07%
Plasma protein binding	94%
Partition co-efficient	115
Molecular weight	274.40
Structure	amide
Maximum dosage	3mg/kg
Lipid solubility	2.8
Volume of distribution	59
Clearance	387+107ml/min
Toxic plasma conc.	111 min

STERESPECIFITY AND STRUCTURE

Enantiomers exist in two different spatial configurations, like right- and left-handed gloves, and are present in equal amounts in a racemic solution. They are optically active and can be differentiated by their effects on the rotation of the plane of a polarised light into dextrorotatory [clockwise rotation (R+)] or levorotatory [counterclockwise rotation (S-)] stereoisomers. The physicochemical properties of the

two enantiomeric molecules are identical, but the two enantiomers can have substantially different behaviours in their affinity for either the site of action or the sites involved in the generation of side effects. R(+) and S(-) enantiomers of local anaesthetics have been demonstrated to have different affinity for different ion channels of sodium, potassium, and calcium; this results in a significant reduction in central nervous system (CNS) and cardiac toxicity (cardiotoxicity) of the S(-)enantiomer as compared with the R(+)enantiomer.[26]

The technological advancements have made it possible to develop Ropivacaine as an optically pure S(-) enantiomeric from the parent chiral molecule propivacaine. It belongs to the group of local anaesthetics, the pipecoloxylidides and has a propyl group on the piperidine nitrogen atom compared to bupivacaine, which has a butyl group.[27]

MECHANISM OF ACTION

Ropivacaine causes reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres.[25] This action is potentiated by dose-dependent inhibition of potassium channels.[28] Ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres; therefore, it has selective action on the pain-transmitting A, β and C nerves rather than Aβ fibres, which are involved in motor function.

PHARMACODYNAMICS

CNS AND CARDIOVASCULAR EFFECTS

Ropivacaine is less lipophilic than bupivacaine and that, together with its stereoselective properties, **[29]** contributes to ropivacaine having a significantly higher threshold for cardiotoxicity and CNS toxicity than bupivacaine in animals[29,30] and healthy volunteers.[31]

The lower lipophilicity of ropivacaine versus bupivacaine correlated with the lesser cardiodepressant effects of both ropivacaine isomers than of the bupivacaine isomers in animal studies.[29]

The CNS effects occurred earlier than cardiotoxic symptoms during an intravenous (IV) infusion of local anaesthetic (10 mg/min of ropivacaine or bupivacaine) in human volunteers and the infusion was stopped at this point. Significant changes in cardiac function involving the contractility, conduction time and QRS width occurred and the increase in a QRS width was found to be significantly smaller with ropivacaine than with bupivacaine.[32, 33]

OTHER EFFECTS

Ropivacaine has been shown to inhibit platelet aggregation in plasma at concentrations of 3.75 and 1.88 mg/mL (0.375% and 0.188%), which correspond to those that could occur in the epidural space during infusion.[34]Like other anaesthetics, ropivacaine has antibacterial activity *in vitro*, inhibiting the growth of *Staphylococcus aureus,*[35,36] *Escherichia coli,*[35] and *Pseudomonas aeruginosa.*[36]

PHARMACOKINETICS

ABSORPTION AND DISTRIBUTION

The plasma concentration of ropivacaine depends on the total dose administered and the route of administration, as well as the haemodynamic and circulatory condition of the patient and vascularity of the administration site.[37]

When ropivacaine was administered intravenously in subjects, its pharmacokinetics were linear and dose proportional up to 80 mg.[37] The absorption of ropivacaine 150 mg from the epidural space is complete and biphasic. The mean half-life of the initial phase is approximately 14 minutes, followed by a slower phase with a mean absorption $t_{1/2}$ of approximately 4.2 hours.

Ropivacaine is bound to plasma proteins to an extent of 94%, mainly to alpa-1 acid glycoprotein. The total plasma concentration increases during continuous epidural infusion of ropivacaine[37,38] and is caused by an increase in the degree of protein binding and subsequent decrease in clearance of ropivacaine.[38]

Ropivacaine rapidly crosses the placenta during epidural administration for caesarean section, resulting in near complete equilibrium of the free fraction of ropivacaine in the maternal and foetal circulation.[39] However, the total plasma concentration of ropivacaine was lower in the foetal circulation than in the maternal circulation, reflecting the binding of ropivacaine to alpha-1 acid glycoprotein, which is more concentrated in maternal than in foetal plasma.

METABOLISM AND EXCRETION

Ropivacaine is metabolised extensively in the liver, predominantly by aromatic hydroxylation to 3'-hydroxy-ropivacaine by cytochrome P450 (CYP) 1A2 and N-dealkylation to 2', 6'-pipecoloxylidide by CYP3A4.[40,41] The kidney is the main excretory organ for ropivacaine, accounting for 86% of the excretion of the drug in urine after a single intravenous dose administration. It has a mean ± SD terminal half-life of 1.8 ± 0.7 h and 4.2 ± 1.0 h after intravenous and epidural administration, respectively.

RELATIVE POTENCY

A strict correlation exists between the lipid solubility of the local anaesthetic and its potency and toxicity. According to minimum local anaesthetic concentration (MLAC) studies, which are based on effective analgesia in 50% of patients) ropivacaine has similar potency to bupivacaine at higher doses (e.g., doses required for peripheral nerve blocks for surgical anaesthesia), ropivacaine is less potent than bupivacaine and levobupivacaine at lower doses, such as those used for epidural or intrathecal analgesia. Providing anaesthesia or analgesia for the majority of patients is more clinically relevant than the MLAC and, at higher doses used in clinical practice, this potency difference is not always evident.

Cardiotoxicity and CNS toxicity in comparison to bupivacaine

The incidence of cardiotoxicity and central nervous system (CNS) toxicity as a result of inadvertent intravascular injection of ropivacaine appears to be low.[45] According to a pooled analysis of data from ≈3000 patients in 60 clinical studies, the incidence of

probable accidental IV injection of ropivacaine was ≈0.2% (six patients) and only one patient experienced convulsions; no patient showed symptoms of cardiotoxicity.[45]

The convulsive local anaesthetic doses of bupivacaine and ropivacaine were studied in different animal models; bupivacaine has a 1.5- to 2.5-fold lower convulsive threshold when compared to ropivacaine. On the basis of animal and volunteer studies, it can be concluded that ropivacaine seems to be less neurotoxic and cardiotoxic than bupivacaine.

DRUG INTERACTIONS

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects of these drugs are additive.

Cytochrome P450 1A2 metabolises ropivacaine to 3-hydroxy ropivacaine, the major metabolite. Thus, strong inhibitors of cytochrome P450 1A2, such as fluvoxamine, given concomitantly during administration of ropivacaine, can interact with ropivacaine and thus lead to increased ropivacaine plasma levels. Caution should be exercised when co-administering CYP1A2 inhibitors. Possible interactions with drugs known to be metabolised by CYP1A2 via competitive inhibition such as theophylline and imipramine may also occur.[46]

CLINICAL USE

It is used for producing central neural axis block (spinal, epidural or caudal)

Infiltrative anaesthesia

Peripheral nerve block

Intravenous regional anaesthesia

DEXMEDETOMIDINE [45]

History

The α_2-adrenergic agonists provide sedation, anxiolysis, hypnosis, analgesia and sympatholysis. The initial impetus for the use of α_2 agonists in anaesthesia resulted from observations made in patients during anaesthesia who were receiving clonidine therapy.

This was soon followed by a description of the minimum alveolar concentration (MAC) reduction of halothane by clonidine. Dexmedetomidine is a more selective α_2 agonist with a 1600 times greater selectivity for the $\alpha_2$receptor compared with the α_1 receptor.

It was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients.

Dexmedetomidine is now being used off-label outside of the ICU in various settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic and procedure units and for other applications such as withdrawal/detoxification amelioration in adult and paediatric patients.

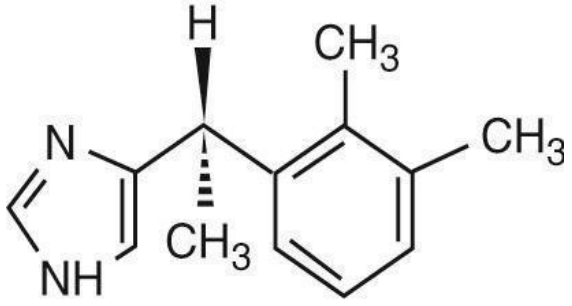

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Figure 8: Dexmedetomidine chemical structure

Physicochemical Characteristics

Pharmacology

Dexmedetomidine is a nonselective α_2 agonist.$\alpha_2$adrenoreceptors are membrane-spanning G proteins. Intracellular pathways include inhibition of adenylate cyclase and modulation of ion channels.Three subtypes of α_2 adrenoreceptors have been described in humans: α_{2A}, α_{2B}, and α_{2C}. The α_{2A} adrenoreceptors are primarily distributed in the periphery, whereas α_{2B} and α_{2C} are in the brain and spinal cord.

Postsynaptic located α_2 adrenoreceptors in peripheral blood vessels produce vasoconstriction, whereas presynaptic α_2 adrenoreceptors inhibit the release of norepinephrine, potentially attenuating the vasoconstriction. The overall response to α_2 adrenoreceptors agonists is related to the stimulation of α_2 adrenoreceptors located in the CNS and spinal cord. These receptors are involved in the sympatholysis, sedation, and antinociception effects of α_2 adrenoreceptors.

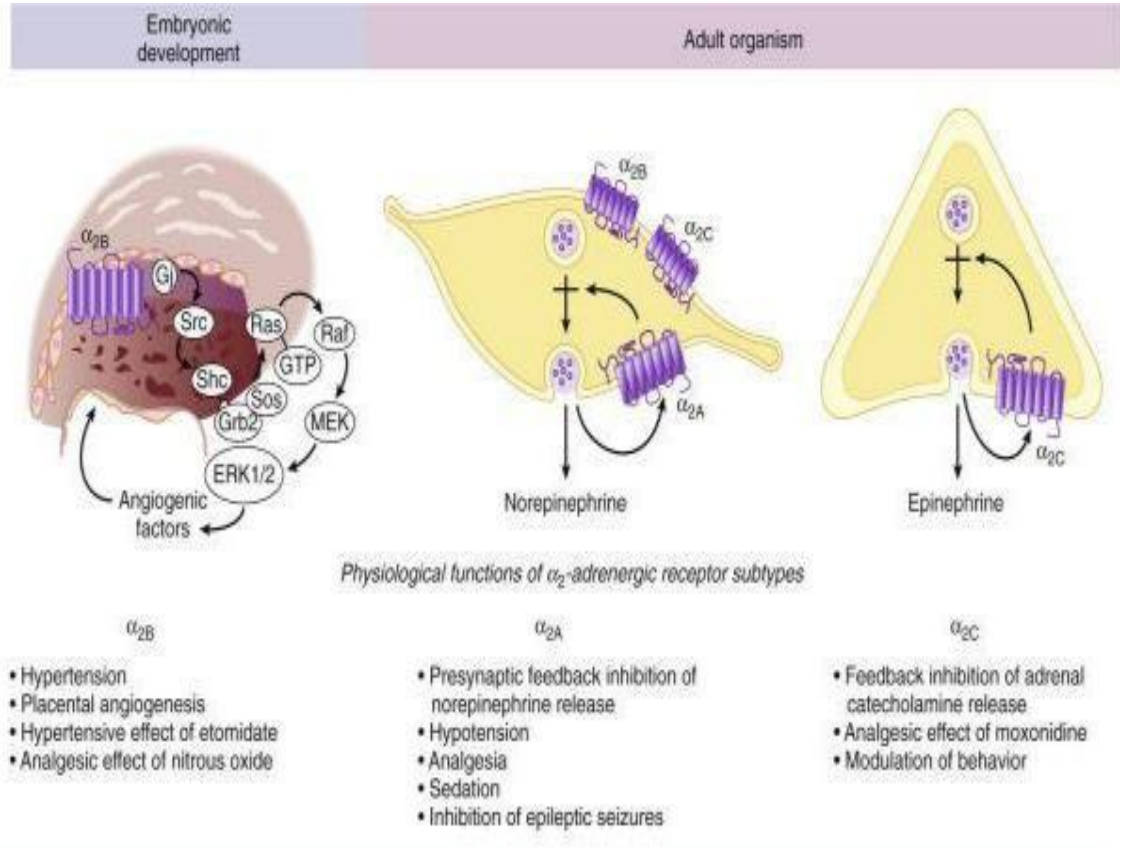


Figure: 9 Physiology of α_2

The different physiologic functions of α_2 adrenoreceptors

The top panel depicts the three α_2 receptor subtypes acting as presynaptic inhibitory feedback receptors to control the release of norepinephrine and epinephrine from peripheral or central adult neurons. Also, a negative feedback loop has been seen in the adrenal gland. Alpha$_{2B}$ receptors have been involved in the development of the placental vascular system during prenatal development. The lower panel lists a series of physiologic effects with its associated $\alpha_2$adrenoreceptors.

Effects on the Central Nervous System

Sedation

The α_2 agonists produce their sedative-hypnotic effect by an action on α_2 receptors in the locus caeruleus and an analgesic action at α_2 receptors within the locus caeruleus and within the spinal cord.

The quality of sedation produced by dexmedetomidine seems different compared with that produced by other sedatives acting through the GABA systems. Patients receiving dexmedetomidine infusions as part of their sedation regimen in the postoperative ICU setting have been described as being very easy to wake up and having the ability to follow commands and cooperate while being tracheally intubated.

Undisturbed, patients were noted to fall asleep right away. Despite sound levels of sedation with dexmedetomidine, there is limited respiratorydepression, providing wide safety margins.This characteristic allows for ―daily wake up‖ tests to be done in a safe fashion. This critical test—when ventilated ICU patients are taken off all sedatives to assess their mental status and titrates sedation—shortens their ventilated and ICU length of stay.

The α_2 agonists act through the endogenous sleep-promoting pathways to exert their sedative effect. Dexmedetomidine produces a decrease in activity of the projections of the locus caeruleus to the ventrolateral preoptic nucleus.This increases GABAergic and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections.

The similarity between natural sleep (non–rapid eye movement) and dexmedetomidine-induced hypnosis has been speculated to maintain cognitive and immunologic function in the sleep-deprived states (as in the ICU). Dexmedetomidine can produce profound sedation, and it has been used as a total IV anaesthetic when given at 10 times the normal sedation concentration range.

The α_2 agonists have the advantage that their effects are readily reversible by α_2-adrenergic antagonists (e.g., atipamezole). Dexmedetomidine can be employed for addiction treatment; dexmedetomidine has been described for use in rapid opioid detoxification, cocaine withdrawal, and iatrogenic induced benzodiazepine and opioid tolerance after prolonged sedation.

Analgesia

The analgesic effects of dexmedetomidine are complex. $Alpha_2$ agonists do have an analgesic effect when injected via the intrathecal or epidural route.Clonidine injected in the neural axis helps with short-term pain, cancer pain, and neuropathic pain. Intrathecally injected dexmedetomidine in sheep reduces blood pressure in 1 minute. When dexmedetomidine is injected into the epidural space, it rapidly diffuses into the CSF (in one study,[22] 22% of the injected dose was identified in the CSF). The effects on blood pressure are slower in onset with an epidural injection than with an intrathecal administration. Epidural effects are seen in 5 to 20 minutes.

The primary site of analgesic action is thought to be the spinal cord.Systemic use of dexmedetomidine shows narcotic sparing. In the postoperative ICU setting, narcotic requirements were reduced by 50% when patients were receiving a dexmedetomidine drip compared with placebo.

Effects on the Respiratory System

In volunteers, dexmedetomidine at concentrations producing significant sedation reduces minute ventilation, but retains the slope of the ventilatory response to increasing carbon dioxide.

Effects on the Cardiovascular System

The basic effects of α_2 agonists on the cardiovascular system are decreased heart rate; decreased systemic vascular resistance; and indirectly decreased myocardial contractility, cardiac output, and systemic blood pressure.

By developing highly selective α agonists, it has been hoped to decrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. The hemodynamic effects of a bolus of dexmedetomidine in humans have shown a biphasic response.

An acute IV injection of 2 µg/kg resulted in an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline that occurred at 5 minutes after injection. This initial increase in blood pressure is probably due to the vasoconstrictive effects of dexmedetomidine when stimulating peripheral α_2 receptors. Heart rate returned to baseline by 15 minutes, and blood pressure gradually declined to approximately 15% below baseline by 1 hour.

The incidence of hypotension and bradycardia may be related to the administration of a loading dose. Omitting the loading dose or not giving more than 0.4 µg/kg reduces the incidence of hypotension, or makes it less pronounced. Giving the loading dose over 20 minutes also minimizes the transient hypertension.

The perioperative use of α_2 agonists reduces the incidence of perioperative myocardial ischemia.A frequently reported side effect of dexmedetomidine has been a dry mouth. Dry mouth is due to a decrease in saliva production.

Uses :

Dexmedetomidine has been approved as a short-term sedative for adult intubated patients in the ICU. Given its well-documented beneficial effects of anxiolysis, sedation, analgesia, and sympatholysis with minimal respiratory depression, it also has been used in various other clinical scenarios.

Intensive Care Unit :

Dexmedetomidine has advantages over propofol for sedation in mechanically ventilated postoperative patients. Dexmedetomidine seemed to have greater recall of their stay in the ICU, but all described this as pleasant overall.α_2-adrenoreceptor agonists have been used in the treatment of alcohol and drug withdrawal. Dexmedetomidine has been successfully used in the treatment of withdrawal of narcotics, benzodiazepines, alcohol, and recreational drugs.The unique characteristics of dexmedetomidine-providing adequate sedation with minimal respiratory depression- can be used when weaning patients from the ventilator. The use of dexmedetomidine to facilitate daily ―wake up‖ tests in mechanically ventilated patients seems attractive, but few data have been published.

Anesthesia :

As a premedicant, dexmedetomidine, at IV doses of 0.33 to 0.67 µg/kg given 15 minutes before surgery, seems efficacious, while minimizing the cardiovascular side effects of hypotension and bradycardia. Within this dosage range, dexmedetomidine

reduces thiopental requirements (by ±30%) for short procedures, reduces the requirements of volatile anaesthetics (by ±25%), and more effectively attenuates the hemodynamic response to endotracheal intubation compared with 2 µg/kg of fentanyl.

Dexmedetomidine also has been evaluated as an IM injection (2.5µg/kg) with or without fentanyl administered 45 to 90 minutes before surgery.Dexmedetomidine has been used for sedation for monitored anesthesia care.

When dexmedetomidine is used as a premedication 10 minutes before general surgery for cataract removal, intraocular pressure is decreased (33%), catecholamine secretion is reduced, perioperative analgesic requirements are less, and recovery is more rapid. Dexmedetomidine can be used for fiberoptic intubation.

CLONIDINE

PHARAMACOLOGY OF CLONIDINE HYDROCHLORIDE [46,47]

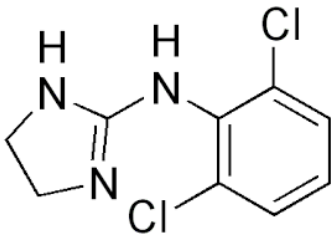


Fig 7 Structure of clonidine

N – (2,6 – dichlorophenyl) -4, 5 –dihydro – 1H – imidazol – z – amine

Clonidine is a direct acting alpha 2 agonist used as an antihypertensive agent. In addition to its antihypertensive effect, in recent studies, clonidine has showed its effective sedative and analgesic properties which reduces the required amount of anaesthetic agents when used as anaesthetic. Therefore, a reconsideration of possible new indications for clonidine in clinical anaesthesiology is justified

PHYSIOCHEMICAL CHARACTERISTICS

Clonidine is a white or almost white crystalline powder. It is soluble in water and in dehydrated alcohol. A 5% solution in water has pH of 4.0 to 5.0.stored in airtight containers at a temperature of 250c, excursion permitted between 150c and 300c.Molecular weight of Clonidine hydrochloride (C9H9CL2N3.HCl) is 266.6.

MECHANISM OF ACTION

ANALGESIA:

Alpha-2 adrenoreceptors are located on primary afferent terminals(both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord, within several brainstem nuclei implicated in analgesia, supporting the possibility of analgesic action at peripheral, spinal and brainstem sites. In contrast to blood, there is a strong correlation between clonidine concentration in cerebrospinal fluid (CSF) and analgesia after clonidine administration. Clonidine is rapidly absorbed into the spinal CSF compartment after epidural administration with concentrations peaking 30-60min after injection. Cerebrospinal fluid is clearly not the site of action of clonidine for analgesia and the drug can reach sites producing analgesia in the spinal cord or elsewhere. As with other lipophilic drugs, it is possible to achieve analgesia from systemic, epidural or intrathecal administration of clonidine. However, clonidine is more potent after neuraxial than systemic administration, indicating a spinal site of action favouring neuraxial administration. This action of clonidine on alpha2-adrenoreceptors has been shown by partial reversal of epidural clonidine‟ s analgesia and sedation by administering the alpha2- adrenergic antagonist, yohimbine although the effects on blood pressure and heart rate were not reversed. There are also suggestions that (in animal studies) clonidine causes analgesia, in part, by spinal

cholinergic activation due to increase in acetylcholine concentrations in the dorsal more than ventral horn in the spinal cord. . Inhibition of substance – p release is also believed to be involved in the analgesic effect. Clonidine also enhances both the sensory and motor blockade from epidural or peripheral nerve block injection of local anaesthetics. Different possible mechanisms have been suggested. First the ability of Clonidine to modify the function of potassium channels in isolated neurons in vitro (cell membranes become hyperpolarized) may be the mechanism for profound decrease in anaesthetic requirements produced by Clonidine. Second clonidine may cause high local vasoconstriction, in clinical setting thereby reducing vascular removal of the local anaesthetic however there is little evidence for this mechanism with the clinically used concentrations

Sedation

Sedation usually accompanies the use of clonidine through its actions on the locus ceruleus. Sedation after epidural clonidine likely reflects systemic absorption and vascular redistribution to higher centers. The quality of sedation produced by alpha 2 agonists differs from sedation produced by drugs (Midazolam, Propofol) that act on gama-aminobutyric acid receptors (GABA). Clonidine acting on alpha2- adrenergic receptors inhibits the sleep regulatory physiological processes in the locus ceruleus via a G-protein mediated mechanism and produces sedation. The result is a calm patient who can be easily aroused to full consciousness. Drugs that activate GABA receptors produce a clouding of consciousness and can cause paradoxical agitation as well as tolerance and dependence.

Clonidine produces dose-dependent sedation over the dose range 50-900mcg of rapid onset (<200min) regardless of route of administration. After a large epidural bolus

dose (700mcg) sedation is intense for 4-6h. In many cases sedation is a desirable property and several studies have demonstrated the reduced need for other sedatives and anxiolytic medications when clonidine is administered intra operatively

Peripheral action of clonidine

Clonidine was initially used for its antihypertensive properties. The central actions are mediated through α_2 adrenoceptors, which are situated at locus coeruleus and dorsal horn of spinal cord. But, specific peripheral effects of clonidine appear to be less obvious because α_2 adrenoceptors are not present on the axon of the normal peripheral nerve. [73] There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. These mechanisms are centrally mediated analgesia, α_2 β adrenoceptor-mediated vasoconstrictive effects, attenuation of inflammatory response and direct action on peripheral nerve. The direct action of clonidine on the nerve can be explained on the basis of a study conducted by Dalle *et al*. They proposed that clonidine, by enhancing activity-dependent hyperpolarisation generated by the Na/K pump during repetitive stimulation, increases the threshold for initiating the action potential causing slowing or blockage of conduction. [48] Kosugi *et al*. examined the effects of various adrenoceptor agonists including dexmedetomidine, tetracaine, oxymetazoline and clonidine, and also an α_2 adrenoceptor antagonist (atipamezole) on compound action potential (CAP) recorded from frog sciatic nerve, and found that CAPs were inhibited by α_2 adrenoceptor agents so that they are able to block nerve conduction. [48]

Haemodynamics

Clonidine affects blood pressure in a complex fashion after neuraxial or systemic administration because of opposing actions at multiple sites. In the nucleus tractus solitarius and locus ceruleus of the brainstem, activation of postsynaptic ά2 – adrenergic receptors reduces sympathetic drive. It also activates non-adrenergic imidazoline – preferring binding sites in the lateral reticular nucleus, thereby producing hypotension and an antiarrthymic action. In the periphery, its action on presynaptic ά2 – adrenoceptors at sympathetic terminals reduce the release of norepinephrine causing vasorelaxation and reduced chronotropic drive. These brainstem and peripheral effects of ά2 - adrenoceptor stimulation are counterbalanced by direct peripheral vasoconstriction through its action on ά1- adrenoceptors from circulating concentrations of clonidine. As a result, the dose – response for clonidine by neuraxial or systemic administration is U-shaped, with peripheral vasoconstriction from circulating drug concentrations at high doses opposing central sympatholysis. In addition to brainstem and peripheral sites of actions, neuraxial administration of clonidine directly inhibits sympathetic preganglionic neurons in the spinal cord. The rather complex action of intrathecally injected α2-adrenergic receptor agonists on hemodynamic variables further depends on the segmental site of injection, the patient's position, the rate of injection, and the temperature of the injected solution. Furthermore, combining α2-adrenergic receptor agonists with local anaesthetics can potentially increase the degree of sympatholysis and resulting hypotension. However, clinical studies in surgical patients on this matter have only infrequently reported increased reductions in arterial BP or heart rate in patients who received both intrathecal clonidine and local anaesthetics.

Clonidine reduces heart rate partly by a presynaptically mediated inhibition of norepinephrine release at the neuroreceptor junction and partly by vagomimetic effect.

Hemodynamic effects of clonidine after neuraxial or systemic administration begin within 30 min and reach maximum within 1-2h and last approximately 6-8 h after a single injection. Delayed onset of hypotension has not been observed with the use of clonidine for analgesia alone or in combination.

Respiratory depression: Alpha sub2-adrenergic agonists do not induce profound respiratory depression even after massive overdose nor do they potentiate respiratory depression from opioids.

Renal: Salt and water retention can occur and is due to reduced sympathetic tone. Conversely a diuretic effect during general anaesthesia has been described after administration of oral Clonidine, 2.5 to 5.0 microgram/kg, as preanaesthetic medication.

GIT: -constipation is also relatively common side effect of Clonidine and incidence is about 10% is due to antisecretory effect on the intestine.

Dermatological: -Rash, erythema, allergic contact dermatitis, angioneurotic edema, urticaria, alopecia and pruritus may occur. Skin reactions have been reported in up to 50% of patients using Clonidine transdermal patches.

Other: -Clonidine prevents opioid induced skeletal muscle rigidity and produces skeletal muscle flaccidity; alpha 2 agonists have no effect on the responses evoked by neuromuscular blocking drugs. Clonidine hydrochloride has been associated with acute attack of porphyria and is considered unsafe in porphyria patients.

PHARMACOKINETICS

Clonidine is highly lipid soluble and hence rapidly absorbed after oral, intravenous and epidural administration. After epidural administration, clonidine is rapidly and extensively absorbed into the spinal CSF compartment, with concentration peaking 30 to 60 minutes after injection. There is a strong correlation between clonidine concentration in the CSF and analgesia after epidural clonidine administration. Epidurally administered clonidine readily partitions into plasma via the epidural veins and attains systemic concentrations (0.5 – 2 ng / ml) that are associated with a hypotensive effect mediated by the central nervous system. After intravenous administration it is readily distributed into extravascular sites including the central nervous system.

Molecular mass 230.093 gm / ml

Bioavailability 75 – 95%

Protein binding 20 – 40%

Volume of distribution 2.1 + 0.4 L / Kg

Elimination T ½ 9 + 2 hours

Onset time 26 + 11 minutes

METABOLISM

In the liver clonidine undergoes hydroxylation to form major metabolite p-hydroxyclonidine. Liver metabolized only 50% of the drug and the remaining

excreted unchanged in the urine. Plasma albumin is the most important protein binding site for clonidine and varies between 20 – 40% in vitro.

SIDE EFFECTS

The most common side effects produced by clonidine are drowsiness, dry mouth, bradycardia and hypotension. It also causes inhibition of orgasm in women. Rebound hypertension can occur after abrupt discontinuation of clonidine therapy (1.2 mg / day) as early as 8 hours and as late as 36 hours after the last dose. Rebound hypertension can usually be controlled by reinstituting clonidine therapy or by administering a vasodilating drug such as hydralazine or sodium nitroprusside.

CLINICAL USE

Hypertension

Treatment of patients with severe hypertension or renin dependent disease . The usual daily adult dose is 0.2 to 0.3 mg orally. Transdermal clonidine patch designed for weekly administration is useful for surgical patients who are unable to take oral medications.

DOSAGE GUIDELINES: CLONIDINE DOSE

Oral - 3-5µg/Kg

Intrathecal - 15µg to 30µg

Epidural - 1µg/kg (or) 50µg . 30 µg /hr (for infusion)

Intravenous - 50 – 75 μg (or) 1μg/kg 15 minutes prior to induction for intubation response attenuation;150 – 300 μg (or) 3 μg / kg for hypertensive crisis; 30 μg given slowly for shivering management.

PREPARATION:

Clonidine is available in 100 microgram and 150 microgram tablets. Also it is available in Injectable form as clear preservative free preparation in1 ml ampoules of 150 microgram.

MATERIAL AND METHODS

After approval from the Institutional Ethical committee and informed written consent from patients, this prospective, randomized, study was carried out in the Department of Anaesthesiology for 1.5 years, SBKS Medical College and Dhiraj Hospital, Piparia, Vadodara, Gujarat.

60 patients aged 18-60 years of either sex , height , weight , ASA status I and II scheduled for elective lower abdominal and lower limb surgeries were enrolled in this study.

INCLUSION CRITERIA:

- Patients in the age range 18-60 years.
- ASA risk category I and II.
- No known history of allergy
- Patient willing to sign informed consent.

EXCLUSION CRITERIA:

- Patient's refusal.
- Patients on antiplatelets, or on anticoagulants therapy
- Patients with local skin infections at site of injection
- Pschycological disorders/Neuropsychiatric disorders.

All the patients were subjected to detailed pre-anaesthetic evaluation with clinical history, **General and Systemic examination** of RS, CVS, CNS & ALIMENTARY SYSTEM.

Routine investigations like Haemogram, Random Blood Sugar, Renal Profile, X ray chest (PA view) and ECG for patients were done.

The aim of this study was to compare the effects of Clonidine 30µg and Dexmedetomidine 5µg added as an adjuvant to Isobaric Ropivacaine 0.75% 3ml for spinal anesthesia. Our study consisted of 60 patients aged between 18-60years, ASA physical status I, II undergoing elective lower abdominal and lower limb surgeries under spinal anaesthesia. They were randomly divided into two groups after obtaining informedconsent.

Group C (n=30) received Inj. Ropivacaine Isobaric 0.75% 3 ml + Inj.Clonidine 30µgm intrathecally.

Group D (n=30) received Inj. Ropivacaine Isobaric 0.75% 3 ml + Inj.Dexmedetomidine 5µgm intrathecally with 0.1ml N.S.

The following parameters were observed & compared.

1. **Onset of sensory and motor block.**
2. **Duration of sensory and motor block.**
3. **Haemodynamic changes during intra & post operatively.**
4. **Duration of analgesia and Rescue Analgesia.**
5. **Side effects and complications during intra & post op(if any).**

Patients were randomly allocated to one of the two groups of 30 patients each .

Group C (n=30) received Inj. Ropivacaine Isobaric 0.75% 3 ml + Inj.Clonidine 30µgm intrathecally to make a total volume of 3.2 ml

Group D (n=30) received Inj. Ropivacaine Isobaric 0.75% 3 ml + Inj.Dexmedetomidine 5µgm intrathecally with 0.1ml N.S to make a total volume of 3.2 ml.

ANAESTHETIC TECHNIQUE:

In pre anaesthesia preparation room, non-invasive monitoring initiated using multipara monitor measuring Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial blood Pressure(MAP), Peripheral oxygen saturation (Spo_2) .Peripheral venous access was secured on hand with 18G cannula and pre-loading with Inj. Ringer Lactate 10-15 ml/kg was initiated. All patients were premedicated with Inj.Glycopyrrolate 0.2mg, ondensetron 4mg IV. in operation theatre.

Under strict aseptic and antiseptic precautions, subarachnoid block was performed in sitting position, using midline approach with 23G spinal needle in L_3-L_4 intervertebral space. After the free flow of CSF, the mixture of drugs according to group was injected.

Immediately after the block, patient was turned supine and assessed for **onset ofsensory and motor blockade** as per the criteria at regularinterval till the **onset of the blockade** was achieved **upto T10 level**.

The **duration of sensory and motor blockade** was assessed at regular intervals.

The sensory block was assessed by skin sensation to pin prick. The motor block was assessed according to the Modified Bromage Scale.

Hemodynamic changes were seen at 0,1,3,5,10,15,30,45,60,90,120,180 minutes

TABLE- 1 : SENSORY AND MOTOR CHARACTERISTICS OF SUBARACHNOID BLOCK

	Onset	**Duration**
Sensory Block	Time duration from end of injection to no response to pin prick up to level of T10	Time duration from onset of block To S2 level
Motor Block	Time duration from end of injection to Bromage scale grade 3 of motor block.	Time duration of regression of motor block to Bromage scale 0

TABLE - 2: MODIFIED BROMAGE SCALE FOR MOTOR BLOCK EVALUATION

Grade 0	The patient is able to move the hip, knee and ankle.
Grade I	The patient is unable to move the hip but is able to move the knee and ankle.
Grade II	The patient is unable to move the hip and knee but able to move the ankle.
Grade III	The patient is unable to move the hip, knee and ankle.

Hemodynamic variables were recorded at0,1,3,5,10,15 then every 15 min for 1 hour & every 30 min upto180 minutes & post op.

Sedation score & VAS score were assessed.

TABLE - 3: THE FOLLOWING RAMASAY SEDATION SCALE WAS USED:

Score	Responses
1	Anxious or restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

Duration of analgesia was considered from the time of onset of sensory block till the first complain of pain (VAS Score >3), when the first dose of rescue analgesic in the form of Inj. Diclofenac Sodium 75 mg intramuscularly was administered.

Figure 11: LINEAR VISUAL ANALOG SCALE was assessed for pain.

0	1 2	3 4 5 6	7 8 9 10
No	**Mild Pain**	**Moderate**	**Severe Pain**

Side effects like nausea, vomiting, hypotension, bradycardia , Rigors, backache & PDPH were recorded intraoperatively and postoperatively and treated accordingly**.**

Hypotension was defined as a fall in systolic blood pressure > 30% of the baseline value or systolic blood pressure < 100 mm Hg and was given intravenous boluses of 6 mg ephedrine and crystalloid fluids with Oxygen via venti mask. Bradycardia was defined as a pulse rate of < 60 beat/ min and was treated with boluse of 0.6 mg atropine. Nausea/vomiting was treated by giving inj. Ondansetron.

STATISTICAL ANALYSIS:

Sample size calculation assuming α error being 0.05 and β error being 0.20 with a power of study 80% showed that 30 patients will be required per study group to detect the deference of at least 30% in the median duration of sensory block between the groups hence we included 30 patients per group.

Data collected was analysed and expressed as mean and standard deviation or numbers and percentages as applicable. Comparison between two groups done using unpaired students t test for quantitative data and chi square test for Qualitative data. P value < 0.05 is considered significant.

OBSERVATION AND RESULTS

STATISTICAL METHODS

Data were collected, tabulated, coded then analysed using SSPS@ Computer version 12.0.

Numerical variables were presented as mean and standard deviation, while categorical variables were presented as percent.

As regard numerical variables, unpaired t test was done. P alue

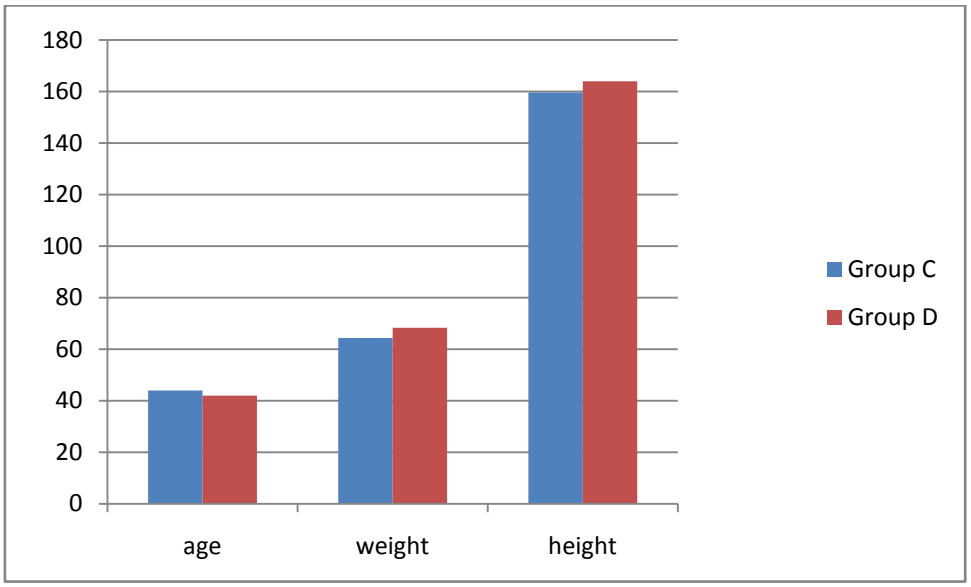
>0.05	**Non Significant**
<0.05	**Significant**
<0.001	**Highly significant**

DEMOGRAPHIC DATA

TABLE 4: AGE, HEIGHT, WEIGHT AND SEX DISTRIBUTION (MEAN ±SD)

Demographic Data	Group C	Group D	P value
Age (years)	43.96±12.03	41.96±12.18	0.4
Weight (kg)	64.4±6.86	68.3±5.4	**0.2**
Height (cm)	159.6±6.90	164±6.28	**0.6**
Gender (M/F)	22/8	164±6.28	**0.6**

Graph 1 : Age , Height and Weight distribution

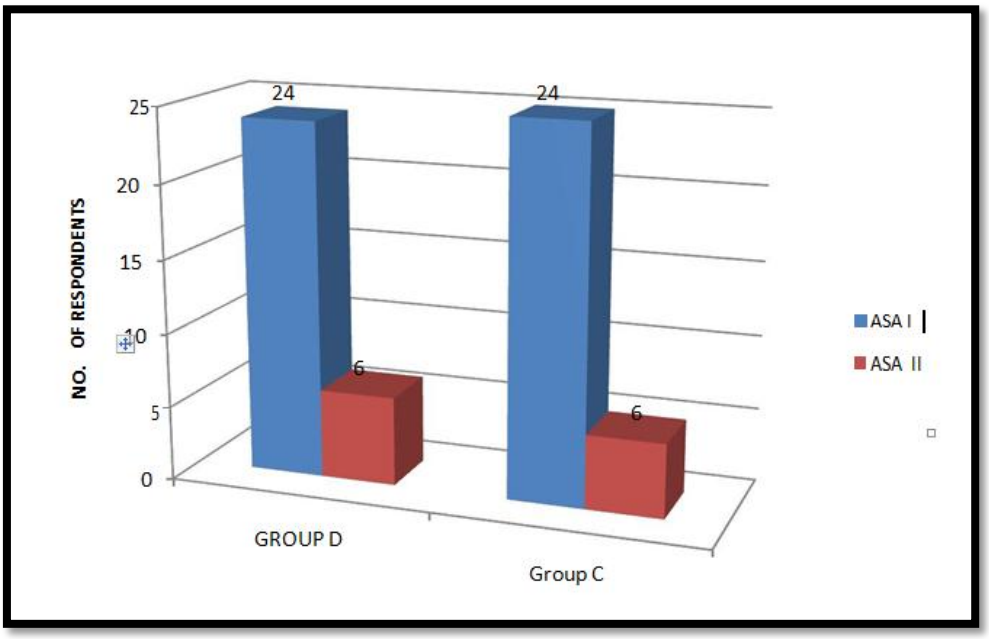


The distribution of patients with respect to age, height, weight & gender were comparable in both the groups. (p value > 0.05) which was statistically non significant.

TABLE 5 : AMERICAN SOCIETY OF ANAESTHESIA (ASA) GRADE

ASA Grade	Group C	Group D
I	24	24
II	6	6

Graph 2: ASA Distribution

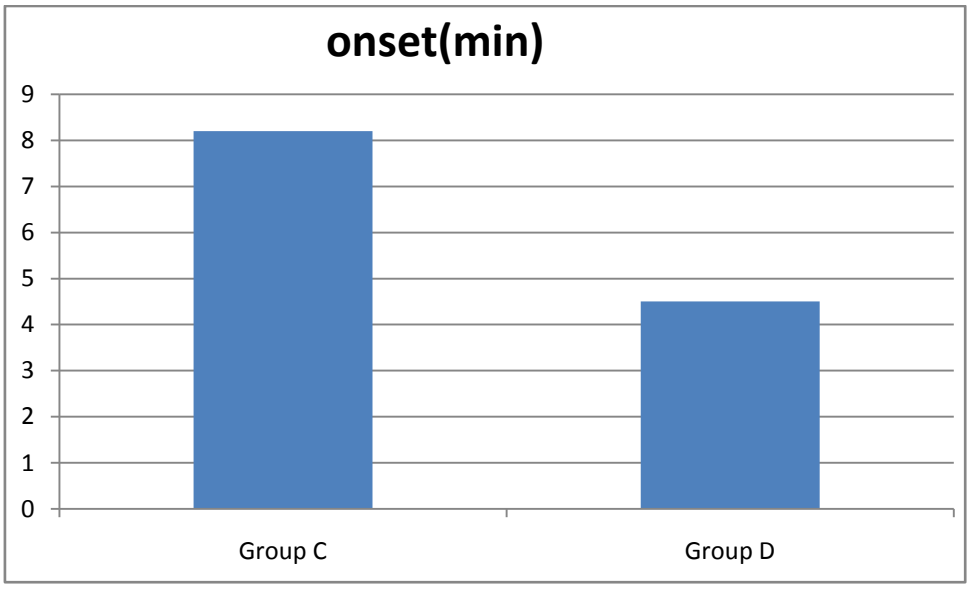


The distribution of patients with respect to ASA grading was comparable in both the groups (p value > 0.05).

TABLE-6 : ONSET OF SENSORY BLOCK

Sensory Block	Group C	Group D	P Value
Onset (in min) Mean±SD	8.2±0.81	4.5±0.50	0.01

Graph 3: Onset of Sensory Blockade

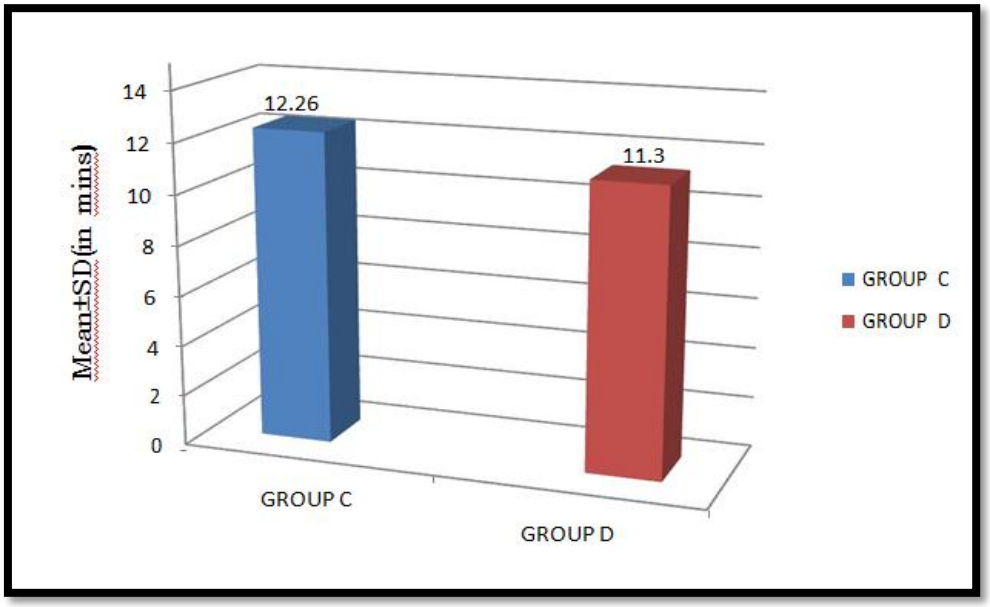


The mean **onset of sensory block** was 8.2±0.81 minutes in group C & in group D 4.5±0.50 minutes which was statistically significant (p value < 0.05).

TABLE-7 : ONSET OF MOTOR BLOCKADE

Motor Block	Group C	Group D	P Value
Onset (in min) Mean± SD	12.26±1.41	11.3±0.87	0.01

Graph 4: Onset of motor block distribution

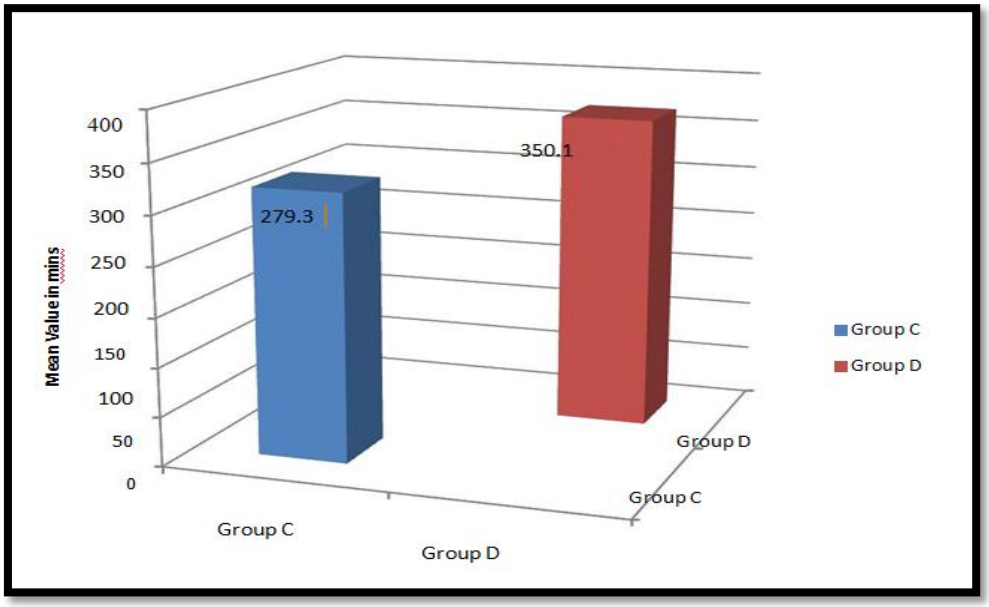


The mean **onset of motor block** in group C was 12.26±1.41 minutes and in group D was 11.3±0.87 minutes which was statistically significant (p value < 0.05).

TABLE-8 : DURATION OF SENSORY BLOCK (MEAN±SD)

Sensory Block	Group C	Group D	P Value
Duration(in min)	279.3±10.7	349.7±7.32	0.04

Graph 5 : Duration of Sensory Block

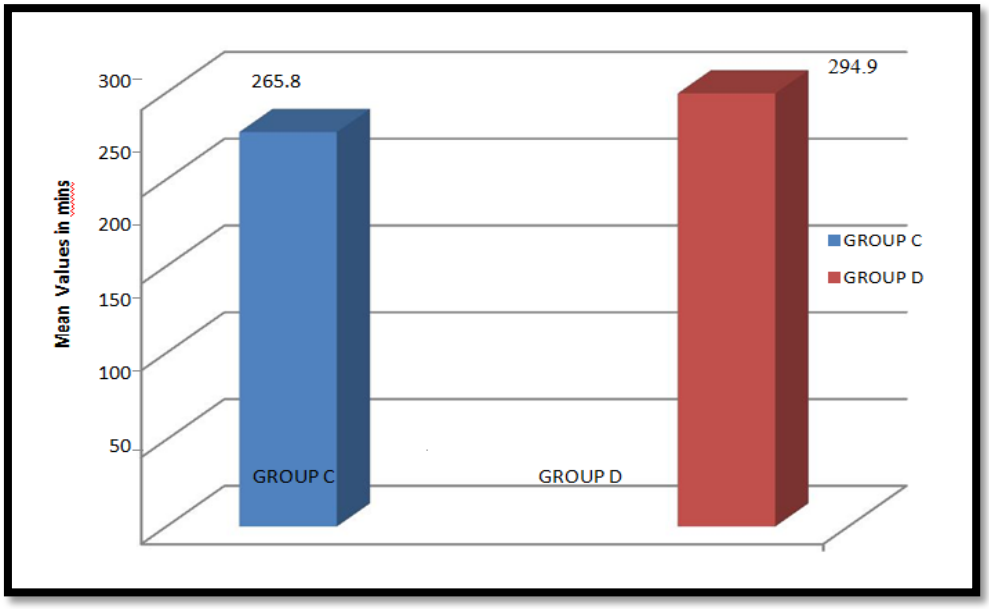


The **Mean duration of sensory blockad**e in group C was 279.3±10.7 minutes and in group D was 349.7±7.32 minutes which was statistically significant (p value < 0.05).

TABLE- 9 : DURATION OF MOTOR BLOCK (MEAN+SD)

Motor Block	Group C	Group D	P Value
Duration(in min)	265.8±11.2	293±7.54	0.03

Graph 6: Duration of Motor Block



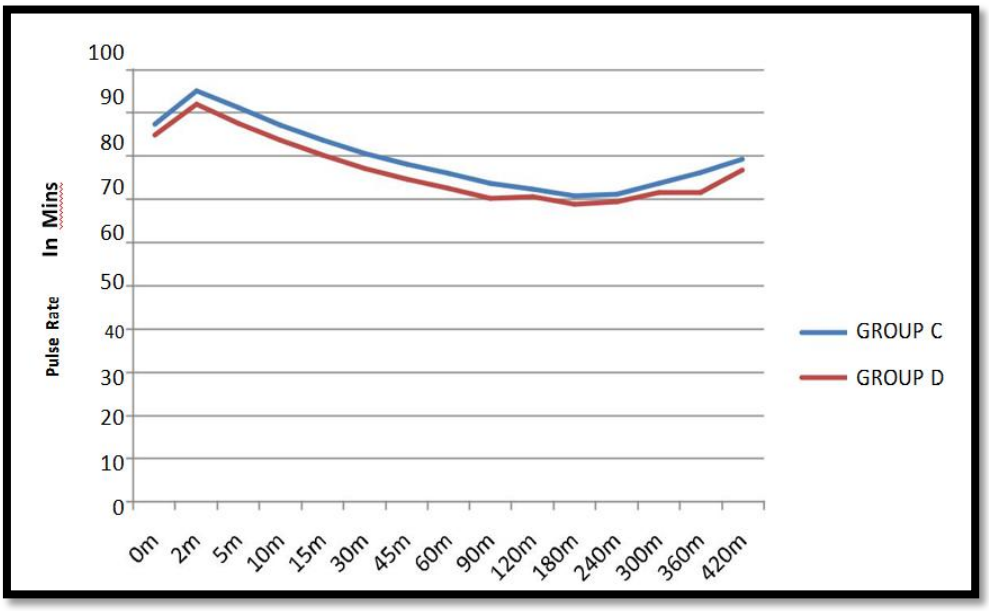
The mean duration of motor blockade in group C was 265.8± 11.2 minutes and in group D was 293±7.54 minutes which is statistically significant (p value < 0.05).

HEMODYNAMIC DATA:

TABLE-10: PULSE RATE (IN MINUTES)

TIME INTERVAL (min)	GROUP C (MEAN±S.D)	GROUP D (MEAN±S.D)	P VALUE	REMARKS
0	84.80±7.05	87.33±7.72	0.18	NS
1	92.03±6.97	94.97±7.37	0.12	NS
3	87.60±7.07	91.17±7.54	0.06	NS
5	83.57±7.20	87.2±7.55	0.06	NS
10	80.13±7.20	83.7±7.75	0.07	NS
15	77.1±7.05	80.60±7.81	0.07	NS
30	74.57±6.87	78.07±7.82	0.06	NS
45	72.52±6.58	75.93±7.86	0.06	NS
60	70.17±6.46	73.7±7.91	0.06	NS
90	70.57±5.85	72.3±7.87	0.33	NS
120	68.9±5.70	70.80±7.98	0.29	NS
180	69.37±5.89	72.33±7.86	0.33	NS

Graph 7: Pulse rate variation



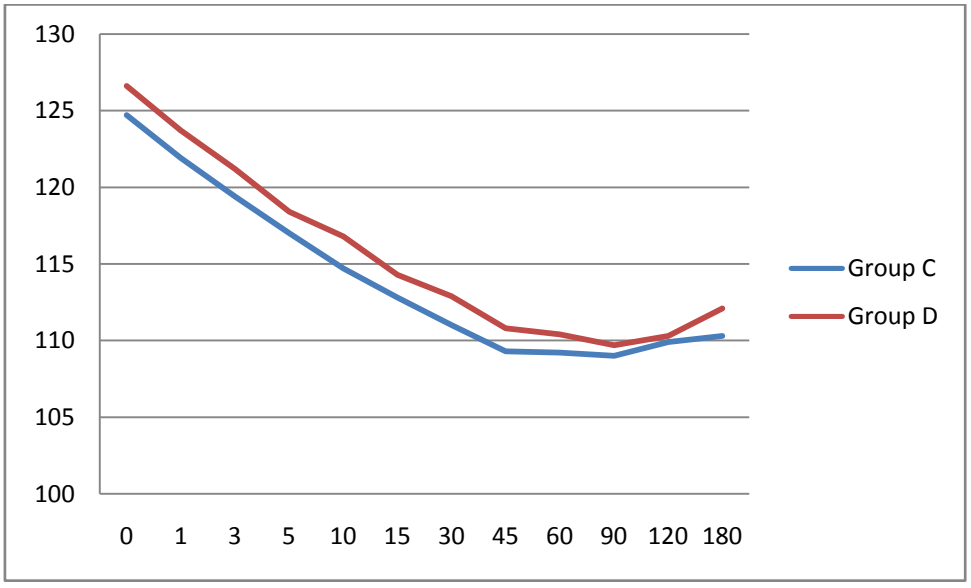
In both the groups a gradual decrease in heart rate was observed from pre -induction values (from 87.33 to 70.80 in group C while in group D from 84.8 to 68.9). But maximum fall was seen at 180 minutes.

Preoperatively no statistically significant difference in pulse rate was seen in between both the groups.(p value>0.05)

TABLE-11: SYSTOLIC BLOOD PRESSURE

TIME INTERVAL (min)	GROUP C (MEAN±S.D)	GROUP D (MEAN±S.D)	P VALUE	REMARKS
0	124.7 ± 7.919131	126.6 ± 9.238911	0.3959	NS
1	121.9 ±7.945287	123.7 ±8.768806	0.3996	NS
3	119.4 ± 7.846296	121.2 ± 8.297902	0.4003	NS
5	117.0 ± 7.748118	118.4 ±7.578023	0.4616	NS
10	114.7 ± 7.003201	116.8 ± 7.098729	0.2610	NS
15	112.8 ± 6.70769	114.3 ± 6.837691	0.4051	NS
30	111.0 ± 6.728649	112.9 ± 6.674363	0.2767	NS
45	109.3 ± 6.506937	110.8 ± 6.343066	0.3592	NS
60	109.2 ± 5.554743	110.4 ± 6.019986	0.4385	NS
90	109.0 ± 5.647601	109.7 ±5.608799	0.6481	NS
120	109.9 ± 5.510804	110.3 ± 5.897594	0.7698	NS
180	110.3 ± 5.317073	112.1 ± 5.475546	0.1856	NS

Graph 8: Systolic blood pressure

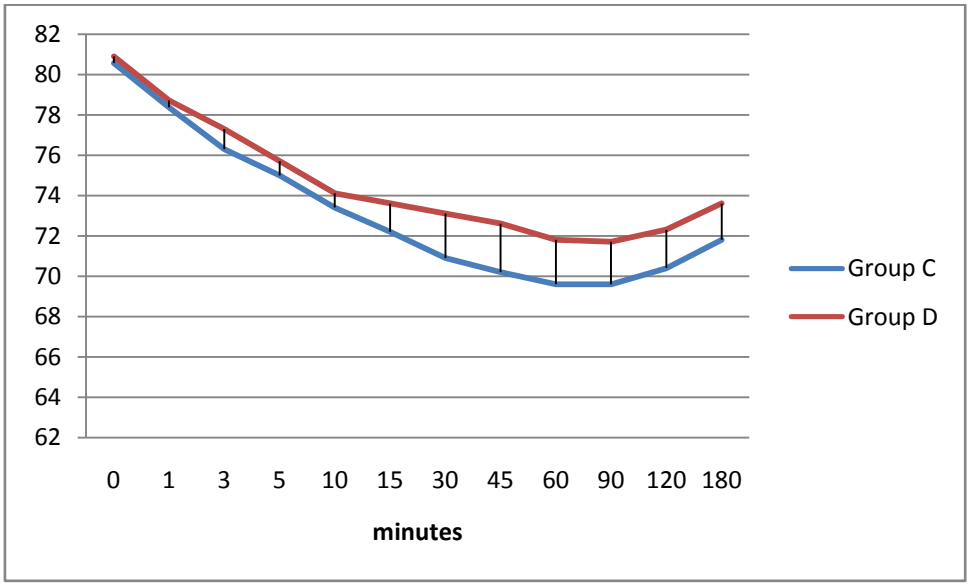


In both the groups a fall in SBP was noted at 15 minutes after induction as compared to pre-induction values (in group C from 124.7 to 114.7 and from 126.6to 116.8 in group D) there was statically no significant change found.

TABLE-12: DIASTOLIC BLOOD PRESSURE

Time Interval (min)	Group C (mean ± SD)	Group D (mean ± SD)	P value	Remarks
0	80.57±6.47	80.93±5.95	0.82	NS
1	78.37±6.01	78.77±6.14	0.79	NS
3	76.30±5.73	77.37±5.83	0.47	NS
5	75.0±5.64	75.77±6.12	0.61	NS
10	73.43±5.99	74.17±5.86	0.63	NS
15	72.27±6.03	73.67±5.65	0.35	NS
30	70.90±5.75	73.17±5.64	0.12	NS
45	70.20±5.57	72.67±5.21	0.08	NS
60	69.63±5.30	71.83±0.92	0.093	NS
90	69.63±0.96	71.47±4.78	0.16	NS
120	70.47±5.13	72.37±4.75	0.13	NS
180	71.87±4.84	73.67±4.80	0.14	NS

Graph 9: Diastolic Blood Pressure variation.

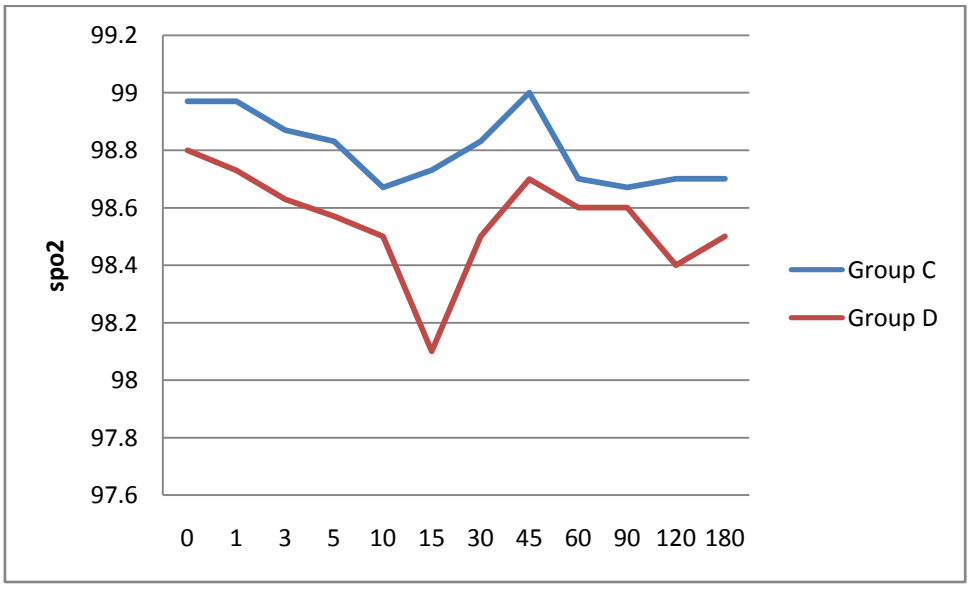


In both groups a fall in DBP was noted at 15 minutes after induction as compared to the pre induction values (from 80.93 to 74.17 in group C, while in group D from 80.57 to 73.43).Diastolic blood pressure in group C compared to group D (p value > 0.05) which was statistically not significant.

TABLE-13: OXYGEN SATURATION (SPO_2)

Time Interval (minutes)	Group C(mean±SD)	Group D(mean±SD)	P value	Remarks
0	98.97±1.03	98.80±1.09	0.54	NS
1	98.97±1.03	98.73±1.08	0.39	NS
3	98.87±0.81	98.63±0.88	0.29	NS
5	98.83±0.87	98.57±1.006	0.35	NS
10	98.67±1.06	98.5±1.04	0.54	NS
15	98.73±0.63	98.13±0.81	0.38	NS
30	98.83±1.03	98.57±1.19	0.36	NS
45	99.0±1.08	98.77±1.21	0.50	NS
60	98.70±1.08	98.63±0.96	0.80	NS
90	98.67±0.99	98.60±1.06	0.80	NS
120	98.7±1.08	98.43±1.19	0.36	NS
180	98.73±0.90	98.57±1.07	0.51	NS

Graph 10: Oxygen Saturation.

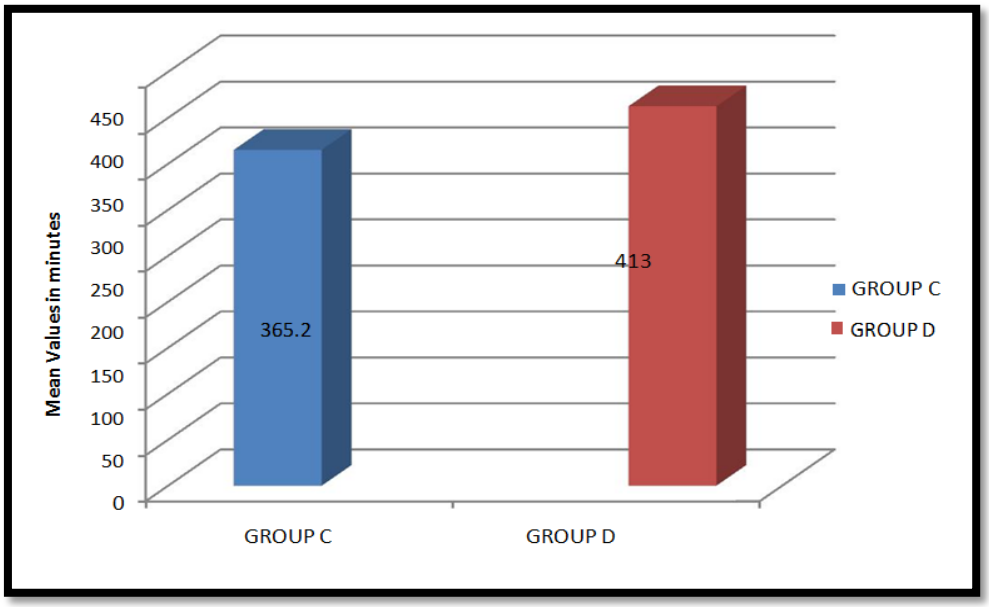


Intra operatively & post operatively difference in SpO2was observed between two groups (p value > 0.05) which was statistically not significant.

TABLE- 14: DURATION OF ANALGESIA (MEAN + SD)

Duration of analgesia (min)	Mean±SD		P Value
	Group C	Group D	0.005
	365.2±8.71	413±5.07	

Graph 11: Mean duration of Analgesia (Mean±SD).



The **mean duration of analgesia** was 365±8.71 minutes in group C and 413±5.07 minutes in group D which shows statistically significant prolongation of duration of analgesia in group D ($p<0.05$) as compared to group C. Duration of analgesia was considered from time of SAB till VAS > 3.

Rescue analgesia was given when VAS > 3.

Ramsay sedation score was 2.

TABLE- 15: COMPLICATIONS OR SIDE EFFECTS

Vomiting	**Group C**	**Group D**
Nausea/vomiting	2 (6.7%)	1(3.3%)
Bradycardia	0	0
Hypotension	0	0
Chest pain	0	0
Rigors	0	0
Headache	0	0
Backache	0	0
Allergic Reactions	0	0

In group C 2(6.7%) and in group D 1(3.3%) patients had nausea/vomiting

No other complications were seen in both groups.

DISCUSSION

Dexmedetomidine hydrochloride, a newer agent having class of alpha-2 receptor agonist, clinically effective sedation with analgesic property for use in intensive care unit. Additionally it has an ability to eliminate or reduce the need for other analgesic medications. Because of its selective alpha2 receptor activity, use of dexmedetomidine has modest and predictable haemodynamic effects, making it a popular sedative and analgesic drug in intensive care unit [47].

It was introduced in clinical practice in the United States in 1999 and approved by the FDA only as a short-term (<24 hours) sedative for mechanically ventilated adult ICU patients. Most of the clinical studies about alpha2 receptor agonists are related to the clonidine.

Clonidine, an α-2 adrenergic agonist potentiates the effect of local anaesthetics and allows decrease in the required doses. Clonidine is a partial α-2 adrenergic agonist used intrathecally with well-established efficacy and safety with effective prolongation of both motor and sensory spinal blockade[9,10,11,12,13]

Dexmedetomidine is now being used off-label outside of the ICU in variety of clinical settings, including sedation and adjunct analgesia in the operating room, sedation in diagnostic procedure and for other applications such as withdrawal/detoxification amelioration in adult and paediatric patients. [45]

Dexmedetomidine is recently being introduced in Indian market; hence to contribute the literature, we decided to study dexmedetomidine in combination with local anaesthetic in subarachnoid block for lower limb and lower abdominal surgery.

Kanazi [19] et al found that intrathecal dose of DXM (3µg) used with bupivacaine for spinal anaesthesia have been shown to produce a rapid onset of motor blockade and a prolongation in the duration of sensory and motor blockade with haemodynamic stability and lack of sedation.

Subhi M Al-Ghanem [3] et al study also winded up that 5µg DXM seems to be a suitable adjuvant to spinal bupivacaine in surgical procedures esp. in long surgeries with minimal side effect and excellent quality of analgesia.

Kalso [17] et al reported a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine.

The above mentioned studies suggest that 5µg dexmedetomidine can be an appropriate dose when used intrathecally.

Hence we found it appropriate to use 5µg preservative free dexmedetomidine with 3ml of 0.75% Ropivacaine intrathecally in our study in comparison with Clonidine 30mcg.

Patients aged between 18 to 60 years in both groups with mean age of 43.96±12.03 years in group C and 41.96±12.18 years in group D

The mean height in group C was 164±6.28 cm and 159.6±6.90 cm in group D

The mean weight of group C was 64.4±6.86 kg and 68.3±5.4 kg in group D

The distribution of patients with respect to ASA grading I/II were 22/8 in group C & 25/5 in group D. $P > 0.05$ not significant.

These parameters were kept identical in both groups to avoid variations in the intra operative and postoperative outcome of the patients.

In our study the mean **onset time of sensory blockade** was in group C 8.2±0.81 minutes compared to groupD 4.5±0.50 minutes P = 0.01 statistically significant.

Mean **onset time of motor blockade** was in group C 12.26±1.41 minutes compared to group D 11.3±0.87 minutes P = 0.01 statistically significant.

Swati Srivastava etal[62] concluded that clonidine with Ropivacaine not only significantly reduces the onset time both of sensory and motor block with 8.76 minutes and 6.8 minutes respectively which was comparable to our study.

Rajni Gupta et al[20] stated thatDexmedetomidine with Ropivacaine reduces the onset time of both sensory and motor block with 4.8 minutes and 11.7 minutes respectively which was comparable with our study.

Alka shah et al[63] reported that Dexmedetomidine with Ropivacaine reduces the onset time of both sensory and motor block with 4.8 minutes and 11.7 minutes respectively which was comparable with our study.

Vidhi Mahendru et al[61] mean time of two segment sensory block regression was 147 ± 21 min in Group BD, 117 ± 22 in Group BC, 119 ± 23 in Group BF, and 102 ± 17 in Group BS ($P < 0.0001$). The regression time of motor block to reach modified Bromage zero (0) was 275 ± 25, 199 ± 26, 196 ± 27, 161 ± 20 in Group BD, BC, BF, and BS, respectively ($P < 0.0001$). The onset times to reach T8 dermatome and modified Bromage 3 motor block were not significantly different between the groups.

In our study we found that **mean duration of sensory block** in group C 279±10.68 minutes and group D 349.7±7.32 minutes P = 0.04 statistically significant.

The **mean duration of motor block** in group C was 265.8±11.2 minutes compared to group D 293±7.54 minutes P = 0.03 statistically significant.

Swati et al[62], concluded that combination of intrathecal 18 mg ropivacaine with 30 mcg Clonidine prolongs the duration of sensory block 248 ± 24.69 minutes and motor block 239.33 ± 23.92 minutes which was comparable with this study.

Yaksh [23] et al, has shown that the intrathecal alpha 2 adrenoreceptor agonist can cause dose dependant decrease in motor strength in animals and prolongation of motor block of spinal anaesthetics due to addition of alpha 2 agonist may result from their binding to motor neurons in dorsal horn.

Kanazi [19] et al showed that the combination of 12 mg of intrathecal bupivacaine with a low dose of 3 µg of dexmedetomidine significantly prolonged the duration of sensory block 303± 75 minutes and motor block 250 ± 76 minutes. In this study we used 22.5mg Ropivacaine with 5µg Dexmedetomidine due to which there was prolongation in duration of sensory and motor block seen.

Subhi M Al-Ghanem [3] et al stated that the addition of spinal bupivacaine with 5 µg DXM significantly increased both sensory (274±73 minutes) and motor block (240±60 minutes) in comparison with sensory (179±47 minutes) and motor blockade (155±46minutes) by intrathecal 25µg fentanyl and bupivacaine in vaginal reconstructive surgery which was similar with our study.

Correa-Sales C[59] et al reported that Intrathecal alpha2 adrenoreceptor agonist produce analgesia by depressing the release of C fiber transmitters and by

hyperpolarisation of post synaptic dorsal horn neurons.[51,52, 53,54,55]. Intrathecal alpha2 receptor agonist have been found to have anti-nociceptive effect for pain. This anti-nociceptive effect may explain the prolongation of sensory block when added to spinal anaesthetic.

In our study, **haemodynamic parameters** like pulse, BP and SPO2 were observed at regular intervals.

In both the groups heart rate was observed from pre induction values and no statistically significant difference in pulse rate between the two groups found.(p value>0.05)

In both the groups a fall in systolic blood pressure and diastolic blood pressure was noted. There was statistically no significant changes in systolic in both the groups maximum at 90 minutes and in group C change was 15mm hg and in D group at 90 minutes and change was 17 mm hg P > 0.05 statistically not significant.

In both the groups diastolic blood pressure was observed from pre induction values and there was no statistically significant difference in diastolic blood pressure between the two groups. P > 0.05

EID MD[57] et al &Mahmoud M. Al-Mustafa[58]et al, revealed that prolongation of spinal block by intrathecal 5µg,10µgor15µg dexmedetomidine did not cause significant effect on blood pressure and heart rate intra-operatively or postoperatively.

Subhi M Al-Ghanem [3] et al reported that the use of intrathecal dexmedetomidine was associated with fall in HR and BP only in few cases and they suggested that this safety profile was due to lower dose of dexmedetomidine used in their study which was similar to our study.

Klimscha W [60] et al revealed that the addition of low dose of alpha2 agonist to local anaesthetics does not further affect the near maximal sympathetic block [48,60] which has been already caused by the dose of local anaesthetic, and hence did not cause significant changes in haemodynamic parameters .

Oxygen saturation was >96% in all the patients intra operatively and post operatively. No statistically significant difference in SpO2 was observed between the groups. (p value>0.05) In our study we found that **mean duration of analgesia** which was calculated as the time period from the administration of study drug till first rescue analgesia was given (VAS ≥3) was 375.6+8.93 minutes in group C and 423+5.72 minutes in group D P < 0.005 statistically significant. At the end rescue analgesia inj. Diclofenac was given.

Rajni gupta[20] et al found that the duration of analgesia in group D was prolonged to 478.4±20.9 minutes and concluded that analgesia was potentiated by addition of dexmedetomidine and their duration was comparable to our study . As we have used less dose of Ropivacaine compared to Rajani gupta study that is why duration is more in their study.

Correa-Sales C[59] et al reported that Intrathecal alpha2 adrenoreceptor agonist produce analgesia by depressing the release of C fiber transmitters and by hyperpolarisation of post synaptic dorsal horn neurons.[51,52, 53,54,55]. Intrathecal alpha2 receptor agonist have been found to have anti-nociceptive effect for both somatic and visceral pain. This anti-nociceptive effect may explain the prolongation of sensory block when added to spinal anaesthetic.

Swati et al[62] concluded that duration of analgesia was prolonged to 405±85.2 minutes and concluded potentiation by addition of clonidine with ropivacaine.

Alka shah et al[63] showed that duration of analgesia was prolonged to 478.4±20.9 minutes and concluded that analgesia was potentiated by addition of dexmedetomidine with Ropivacaine and their duration was comparable to our study.

The sedation score was assessed using Ramsay sedation score at regular intervals. The dose of dexmedetomidine selected in this study did not produce excessive sedation as at no time sedation score exceeded 2.

Sedation score was comparable with time period in both the groups and no statistically significant difference was seen (p value>0.05)

Subhi M Al-Ghanem [3] bupivacaine and found patients.

Mahmoud M. Al-Mustafa [58] et al studied the effect of spinal bupivacaine combined with normal saline(N), Dexmedetomidine 5µg(D5) or 10µg(D10) and found that all the 3 groups had a maximum sedation score 2.

The incidence of **side effects** like nausea, vomiting, bradycardia and sedation were comparable in both the groups and were not significant.

In the present study, 2 (6.7%) patient had nausea/vomiting in group C compared to 1 (3.33%) patient in group D which was treated with inj.ondansetron.

Eid MD[57] et al found that dexmedetomidine group had only 2 patient having nausea/vomiting in their study on intrathecal dexmedetomidine.

Mahmoud M. Al-Mustafa[58] et al found that in intrathecal dexmedetomidine10µg group 1 patient had nausea/vomiting and 1 patient had hypotension, while in DXM 5 µg group 1 patient had bradycardia, which was not significant.

Swati et al[62] found that in intrathecal clonidine 30µg 5 patient had nausea/vomiting which was not significant.

Hence in the present study, the use of 5µg Dexmedetomidine as an adjuvant to Ropivacaine in spinal anaesthesia produces early onset and prolonged the duration of sensory and motor blockade and duration of analgesia as compared to 30µg Clonidine, with minimal changes in haemodynamic parameters and SpO2 without significant sedation and adverse effects .

Because of lack of any adverse effects, we recommend the routine use of 5µg dexmedetomidine as an adjuvant to Ropivacaine in subarachnoid block when the prolongation of spinal anaesthesia is desired.

CONCLUSION

We concluded that the supplementation of 3ml of spinal 0.75% Ropivacaine with 5µg dexmedetomidine significantly shortens the time of onset and prolonged the duration of sensory and motor blockade into the postoperative time as compared to intrathecal 0.75% Ropivacaine with 30µg Clonidine, and hence provided effective potentiation of postoperative analgesia. The haemodynamic parameters and SpO2 were comparable with minimal changes in both the groups. Minimal sedation & VAS score with no significant side effects/complications were seen.

SUMMARY

The study was conducted to compare the effect of intrathecal Isobaric Ropivacaine 0.75% with Dexmedetomidine 5µg preservative free and intrathecal Isobaric Ropivacaine 0.75% with Clonidine 30µg in lower abdominal and lower limb surgeries.

60 patients belonging to ASA I/II, aged between 18 years and 60 years of either sex posted for elective lower abdominal and lower limb surgeries were randomly allocated for the study.

Group C (n=30) received Inj. Ropivacaine Isobaric 0.75% 3 ml + Inj.Clonidine 3oµg intrathecally to make a total volume of 3.2ml .

Group D (n=30) received Inj. Ropivacaine Isobaric 0.75% 3 ml + Inj.Dexmedetomidine 5µg intrathecally with 0.1ml N.S to make a total volume of 3.2 ml .

The patients studied across the groups didn't vary much with respect to age, sex, weight, height and ASA classification (p value >0.05).

In our study the mean **onset time of sensory blockade** was in group C 8.2±0.81 minutes compared to groupD 4.5±0.50 minutes P = 0.01 statistically significant.

Mean **onset time of motor blockade** was in group C 12.26±1.41 minutes compared to group D 11.3±0.87 minutes P = 0.01 statistically significant.

In our study we found that **mean duration of sensory block** in group C 279±10.68 minutes and group D 349.7±7.32 minutes P = 0.04 statistically significant.

The **mean duration of motor block** in group C was 265.8±11.2 minutes compared to group D 293±7.54 minutes P = 0.03 statistically significant.

The **mean duration of analgesia** which was calculated as the time period from the administration of study drug till first rescue analgesia was given(VAS ≥3) 375.6+8.93 minutes in group C and 423+5.72 minutes in group D.

P < 0.005 statistically significant.

Haemodynamic parameters (HR, SBP and DBP) and SpO_2remained withinnormal limits and were comparable in both the groups (p value>0.05).

The **sedation score** was 2 in all the patients and proved desirable as all the patients remained calm and quite during surgery.

Side effects-In group C 2(6.7%) and in group D 1(3.3%) patients had nausea/vomiting 1(3.3%) which was treated with inj. Ondansetron

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ANNEXURES

ANNEXURE A : ABBREVIATIONS

ANNEXURE B : STUDY PROFORMA

ANNEXURE C : PARTICIPANT INFORMATION SHEET

ANNEXURE D : INFORMED CONSENT FORM

ANNEXURE E : MASTER CHART

LIST OF ABBREVIATIONS USED

%	-	Percentage
ASA	-	American Society of Anesths\esiologists
BP	-	Blood Pressure
CNS	-	Central Nervous System
DBP	-	Diastolic Blood Pressure
Group D	-	Group Dexmedetomidine
Group F	-	Group Fentanyl
hr	-	Hours
HR	-	Heart Rate
IV	-	Intravenous
lit	-	Litre
M	-	Molar
MAP	-	Mean arterial pressure
Mcg	-	Microgram
mg	-	Milligram
min	-	Minute
ml	-	Millilitre
O_2	-	Oxygen
ORTHO	-	Orthopaedics
pts	-	Patients
RR	-	Respiratory Rate
SBP	-	Systolic Blood Pressure
SPO_2	-	Peripheral Arterial Oxygen Saturation
Sec	-	Second
SD	-	Standard Deviation
URO	-	Urology
V_d	-	Volume of Distribution
yr	-	Year

PROFORMA

Pre – Anaesthetic check up:

Identification –

- Name – IPD No.-
- Age/sex - Weight –
- Height- ASA-
- Diagnosis – Operation –
- Past history –
- Drug allergy -
- Operative history –
- Personal history –
- Smoking – Alcohol –
- Diet – Bowel / bladder –

General examination –

- GC – Temperature –
- Pulse – Blood pressure –
- LMP – Pallor –
- Icterus – Clubbing –
- Cyanosis – Edema –
- Lymphadenopathy –

Systemic examination –

- R.S. – CVS –
- CNS – AS –

Investigations –

- Haemoglobin%- Total count-
- Differential count- Platelets-
- Erythrocyte sedimentation rate-
- Bleeding time and Clotting Time- Fasting blood sugar-
- Blood urea- Serum creatinine-
- Urine analysis-
- Chest X-ray-
- ECG-
- HIV and HbsAg-
- USG-

Intra – operative:

- Pre – medication : Anaesthetist :
- Spinal anaesthesia (drug): Ropivacaine + _____
- Time of spinal anaesthesia : Surgeons:
- Time of surgery :
- Intra – operative findings :

Vitals/Time (mins)	0	1	3	5	10	15	30	45	60	75	90	105	120	180
Pulse														
BP														
SpO_2														
RR														
Level														
Sedation score														
Input														
Urine Output														

Post –operative –

- Level –
- Pulse –
- Blood pressure –
- SpO_2 -
- Analgesia score (Visual Analogue Scale) –

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**

- Severe Pain
- Moderate Pain
- Mild Pain
- No Pain

Sedation score (Ramsay Sedation Scale) –

Score	Response
1	Anxious or restless or both
2	Cooperative, oriented and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

- Total Duration of Sensory Block -
- Total Duration of Motor Block-
- Total Duration of Post- Op Analgesia-
- Complications –

INFORMED CONSENT FORM

(To be taken in vernacular from each subject)

I _____ son / daughter / wife of _____ understand that there are no serious side effects of any of the drugs /methods to be used in the study. However the possibility of any of unknown side effects of these drugs/methods has been explained to me. I therefore voluntarily agree to participate in the study of **"COMPARATIVE STUDY OF INTRATHECAL ISOBARIC ROPIVACAINE 0.75% WITH**

DEXMEDETOMIDINE ANDCLONIDINE AS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES"I have been explained that I am free to withdraw from the study at any time without any terms and conditions.

Dr. In charge Signature of the Subject

Dated:

Witness:

અભ્યાસમાં ભાગ લેવા માટે સમજી વિચારીને આપેલી પરવાનગી નુ સમ્મતિ - પત્રક

અભ્યાસનુ નામ: "OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF ISOBARIC ROPIVACAINE 0.75% WITH DEXMEDETOMIDINEANDCLONIDINE AS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMB AND LOWER ABDOMINAL SURGERIES"

અભ્યાસક્રમાંક:_____ તારીખ:_____

સહભાગીનુપુરું નામ:_____

સહભાગીનુટુંકુનામ:_____

સહભાગીની જન્મ તારીખ / ઉંમર: _____

૧. હું ખાત્રી આપું છું કેમે ઉપરોક્ત અભ્યાસની (તા: / /)
માહિતીવાંચીછેઅનેસમજીછેઅનેતેઅંગેનામુંઝવતાપ્રશ્નોપુછવાનીમનેતકઆપવામાઆવીછે

૨. હુંજાણુંછુંકેઆઅભ્યાસમાંભાગલેવોમારામાટેમરજીયાતછેઅને,
કોઇપણજાતનુકારણઆપ્યવગર, તેમાથીગમેત્યારખસીજવાનીમનેછૂટછે,
અનેઆમકરવાથીમારીતબીબીસારવારકેકાયદેસરનાહક્કોનેકોઇઅસરનહીંથાય.

૩. હુંજાણુછુંકેઆઅભ્યાસનાતપાસકર્તા, તેમનામદદનીશો,
એથિકલટીમઅનેતેનાઉપરદેખરેખરાખતાઅધિકારીઓનેમારાસ્વાસ્થ્યનીકોઈપણજાતનીમા
હિતી, સદરઅભ્યાસનેલગતીકેતેસિવાયની, મેળવવામાટેમારીપરવાનગીનીજરૂરરહેશેનહીં,
ભલેપછીહુંઅભ્યાસમાંથીખસીજાઉં.
હુંજાણુંછુંકેમારીઆપ્રકારનીમાહિતીઅન્યકોઇનેજાણકેપ્રસિધ્ધનહીંકરવામાંઆવે.

૪.આઅભ્યાસદરમ્યાન, અથવાતેનાઅંતેપ્રાપ્તથતીમાહિતી,
કોઈપણજાતનીવૈજ્ઞાનિકશોધમાટેઉપયોગકરવામાટેહુંસ્વૈચ્છિકરીતેછુટઆપુંછું.

૫. હુંઆઅભ્યાસમાંભાગલેવા / જોડાવામાટેસહમતિઆપુંછું.

અભ્યાસમાંભાગલેનારનીસહિઅથવાઅંગુઠાનુનિશાન:_____તારીખ:_____
_

કાયદેસરનાસ્વિકૃતતપાસકર્તાનીસહી: _____તારીખ:_____

તપાસકર્તાનુનામ: _____

તટસ્થસાહેદ / ગવાહનીસહી: _____તારીખ:_____

તટસ્થસાહેદ / ગવાહનુનામ: _____

સહભાગીમાહિતીપત્રક

અભ્યાસનુનામ: "OBSERVATIONAL STUDY TO COMPARE THE EFFECT OF ISOBARIC ROPIVACAINE 0.75% WITH DEXMEDETOMIDINE ANDCLONIDINEAS AN ADJUVANT IN SPINAL ANAESTHESIA IN LOWER LIMBAND LOWER ABDOMINALSURGERIES"

અભ્યાસક્રમાંક:_____ તારીખ:_____

આમંત્રણ

૧. અભ્યાસનોપ્રકારઅનેહેતુ:

૨. સ્વૈચ્છિકસહભાગિતા:અભ્યાસમાંભાગલેવોસંપુર્ણપણેમરજિયાતછે.

૩.

અભ્યાસનીરીત:અભ્યાસમાંસામેલદર્દીઓનુવિગતવારફરિયાદોઅનેતપાસનારિપોર્ટપરથી મૂલ્યાંકનકરવામાઆવશે. તેમનાલોહીનીતપાસકરવામાઆવશે. એકઠીથયેલીવિગતોનુવિવિધમાપદંડવડેપૃથક્કરણકરવામાઆવશે.

૪.

સહભાગીનીજવાબદારી:અભ્યાસમાંભાગલેવામાટેસહમતથયાપછીસહભાગીએતપાસકર્તાને તમામસુસંગતતથ્યોતેમજતપાસમાંસંપૂર્ણસહકારઆપવોપડશે.

૫. અંદાજીતઆડઅસર,

જોખમઅનેતેનોઉકેલ:આઅભ્યાસમાંસહભાગીપરકોઈપ્રયોગકેઅખતરાકરવામાઆવતાનથી , તેથીકોઇજોખમકેઆડઅસરનીસંભાવનાનથી.

૬. સહભાગિતાનોલાભ:આઅભ્યાસમાંભાગલેવાથીસહભાગીનેતેનારોગવિષેમાહિતીમળશે, જેનોલાંબાગાળેતેનાસારવારમાફાયદોથશે.
આરોગવિષેવધારેમાહિતીમળવાથીસમાજનેપણતેલાભદાયીથશે.

૭. માહિતીનીગોપનીયતા:

સહભાગીનીએકઠીકરેલતમામમાહિતીગોપનીયરાખવામાઆવશે.

૮. કોઇપણપ્રકારનીતકલીફમાટેસંપર્ક

Dr ASHISH TYAGI, (M) 07041552128

Room no.72, NRI BOYS HOSTEL, Sumandeep Vidyapeeth, Piparia,

Taluka: Waghodia, District: Vadodara.

૯.

આર્થિકવિકલ્પઃસહભાગીનેરુધિરાભાવનારોગનેસુસંગતતપાસસિવાયઅન્યકોઈતપાસનોઆર્થિકબોજનહિઆપવામાઆવે.

૧૦.

સહભાગીનીસલામતિઃઉપરોક્તઅભ્યાસનેસુસંગતકોઈપણપ્રકારનાઅણબનાવસામેસહભાગીનેયોગ્યરક્ષણપુરૂપાડવામાઆવશે.

જરૂરપડ્યેવધારાનીમાહિતીમાટેસહભાગીનોસંપર્કકરવામાઆવશે

Protocol No.: XXXXXXX

Protocol No.: XXXXXXX

Patient Information Sheet and Consent Form

PATIENT INFORMATION SHEET

Study Title: Observational study to compare the effect of Isobaric Ropivacaine 0.75% withdexmedetomidineand clonidine as an adjuvant in spinal anaesthesia for lower limb and lower abdominal surgeries.

- Introduction:

  Brief introduction of study- this is an observational study where it will be proven

  That which drug combination has more prolonged & better effect in spinal anaesthesia for lower abdominal & lower limb surgeries.

- What is the purpose of this study?- For good quality & potentiation of post operative analgesia.

- Why have I been chosen?- It is a safer and better anaesthetic agent with less side effects than the older anaesthetic agents . you are an ASA ½ fit patient undergoing an elective lower abdominal / lower limb surgery.

- Do I have to take part? -Yes, after understanding all the merits or demerits of this study

- How long will the study last? – Over a period of 2 years.

- What will happen to me if I take part?-Your identity and details will be confidential.

  - *Screening Period: a pre- anaesthetic check up will be performed and the procedure will be explained with informed consent.*

  - *Treatment Period: will go on as long as the surgery lasts.*

  - *Allocation of investigational product:we know which drug we are giving to patient.*

  - *Follow-up period:will be followed up every 2hrly till first complain of pain &once patient complains of pain,study ends with rescue analgesia.*

- What do I have to do?- understand the nature of this study and agree to be a part of this study

- What is the drug being tested?-Dexmedetomidine & Clonidine with Ropivacaine.

- What are the benefits of the study?-Safer & better traditional anaesthetic agent with less side effect & good quality with prolonged duration of analgesia.

- What are the alternatives for treatment? - Nil

- What are the side effects of the treatment received during the study?-No significant side effect.

- What if new information becomes available? -The participant will be the first one to be updated.

- What happens when the study stops?- The study results will be confidential and the participant will be informed.

- What if something goes wrong? – an entire skilled and trained team of anaesthetist is always available in the operation theatre for that.

- Will my taking part be kept confidential?- yes

- What else should I know?- You are going to be a part of a research project of a post graduate resident & will be under a very well expertised,skilled& experienced anaesthetist throughout the study.

- Additional Precautions – all emergency drugs & equipment will be kept ready & preloading will be done.

- Who to call with questions?-You can contact DR.ASHISH TYAGI phone no:7041552128. Room no 72 nri boys hostel sumandeep vidyapeeth university ,pipariya.

  Protocol No.: XXXXXXXX

INFORM **CONSENT**

Study Title: Observational study to compare the effect of Isobaric Ropivacaine 0.75% with dexmedetomidineand clonidine as an adjuvant in spinal anaesthesia for lower limb and lower abdominal surgeries.

StudyNumber:

Subject's Initials:

Subject's Name:

Date of Birth / Age:

Address of the Subject:

Qualification:

Occupation: Student/ Self-Employed/ Service/ House-wife/Others:

(Please tick as appropriate)

Annual Income of the subject:

Details of Nominee (s):

Name of Nominee:

Address of Nominee:

Relation to Subject:

Please initial box (Subject)

I confirm that I have read and understood the information sheet dated ……....….for the above study and have had the opportunity to ask questions.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/LAR:

Date: / /

Signatory's Name:

Signature of the Investigator:

Date: / /

Study Investigator's Name:

Signature of the Witness

Date: / _/

Name of the Witness:

Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject or his/her attendant.

પ્રોટોકોલ કોઈ .: XXXXXXX

દર્દી માહિતી શીટ અને સંમતિ ફોર્મ

દરદી માિહતી શીટ

અભ્યાસમાં શીર્ષક: ઓબ્ઝર્વેશનલ અભ્યાસમાં નીચલા પેટનો અને નીચલા અંગ શસ્ત્રક્રિયા માટે કરોડરજ્જુ એનેસ્થેસિયાના એક સહાયક તરીકે dexmedetomidine અને clonidine સાથે Isobaric Ropivacaine 0.75% અસર સરખાવવા માટે.

પરિચય:

અભ્યાસમાં- આ સંક્ષિપ્ત પરિચય તે સાબિત થશે જ્યાં એક નિરીક્ષણ અભ્યાસ છે

કે જે ડ્રગ સંયોજન નીચલા પેટનો & નીચલા અંગ શસ્ત્રક્રિયા માટે કરોડરજ્જુ એનેસ્થેસિયાના વધુ લાંબી અને સારી અસર પડે છે.

શું આ અભ્યાસના હેતુ છે -? સારી ગુણવત્તા અને પોસ્ટ ઓપરેટિવ પીડાનો અભાવ ના પાવરઆમાટે.

હું પસંદ કરવામાં આવ્યા છે શા? - તે જૂની એનેસ્થેટિક એજન્ટો કરતા ઓછી આડઅસરો સાથે સુરક્ષિત અને વધુ સારી એનેસ્થેટિક એજન્ટ છે. તમે એક વૈકલ્પિક નીચલા પેટનો / નીચા ગાત્ર શસ્ત્રક્રિયા પસાર એક ASA સાડા ફિટ દર્દી છે.

હું ભાગ લેવા માટે હોય છે? હા, આ અભ્યાસ તમામ ગુણવત્તાના અથવા અવગુણસમજવામાં પછી

અભ્યાસ ક્યાં સુધી ચાલશે? - 2 વર્ષના સમયગાળામાં બોલ.

હું ભાગ લેવા તો મને શું થશે? -તમારા ઓળખ અને વિગતો ગુપ્ત રહેશે.

સ્ક્રિનિંગ સમય: એક પૂર્વ એનેસ્થેટિક ચેક અપ કરવામાં આવશે અને પ્રક્રિયા જાણકાર સંમતિ સાથે સમજાવી કરવામાં આવશે.

સારવાર સમય: સુધી સર્જરી ચાલે તરીકે પર જાય છે.

શોધરૂપી ઉત્પાદન ફાળવણી: અમે અમે દર્દીને આપ્યા છે જે દવા ખબર.

અનુવર્તી સમયગાળા: પ્રથમ પીડા ફરિયાદ & દર્દી પીડા ફરિયાદ વાર, અભ્યાસ રેસ્ક્યૂ પીડાનો અભાવ સાથે અંત થાય ત્યાં સુધી 2hrly દરેક અનુસરવામાં આવશે.

હું શું કરવા હોય -? આ અભ્યાસ પ્રકૃતિ સમજવા અને આ અભ્યાસના એક ભાગ બનવા માટે સંમત

શું આ ડ્રગ Ropivacaine સાથે? -Dexmedetomidine & Clonidine પરીક્ષણ કરવામાં આવી રહી છે.

અભ્યાસ ના લાભો કયા છે? -સુરક્ષિત&ઓછી આડઅસર & પીડાનો અભાવ લાંબા સમયગાળા સાથે સારી ગુણવત્તા સાથે વધુ પરંપરાગત એનેસ્થેટિક એજન્ટ.

સારવાર માટે વિકલ્પો કયા છે? - શૂન્ય

શું અભ્યાસ દરમિયાન મળેલી સારવારની આડઅસર છે? -કોઈ નોંધપાત્ર આડઅસર.

શું નવી માહિતી ઉપલબ્ધ બને તો શું? -ધ સહભાગી સુધારવાની પ્રથમ એક હશે.

આ અભ્યાસ પરિણામો ગુપ્ત રહેશે અને સહભાગી જાણ કરવામાં આવશે - શું અભ્યાસ અટકે ત્યારે થાય.

શું કંઈક ખોટું થાય તો? - નિશ્ચેતનકર્તા એક સમગ્ર કુશળ અને પ્રશિક્ષિત ટીમ હંમેશા તે માટે પ્રક્રિયાને થિયેટર માં ઉપલબ્ધ છે.

મારા લેવાથી ભાગ ગુપ્ત રાખવામાં આવશે? - હા

હું બીજું શું જાણવું જોઈએ? - તમે એક પોસ્ટ ગ્રેજ્યુએટ રહેવાસી એક સંશોધન પ્રોજેક્ટ એક ભાગ હશે આવે છે અને અભ્યાસ દરમિયાન ખૂબ જ સારી રીતે નિપુણતા, કુશળ અને અનુભવી નિશ્ચેતનકર્તા હેઠળ રહેશે.

વધારાની સાવચેતી - બધા કટોકટી દવાઓ અને સાધનો તૈયાર રાખવામાં આવશે અને પહેલાથી લોડકરવામાં આવશે.

પ્રશ્નો સાથે કોને કૉલ કરો 'તમે DR.ASHISH ત્યાગી ફોન કોઈ સંપર્ક કરી શકો છો:? 7041552128. ઓરડામાં કોઈ 72 એનઆરઆઈ છોકરાઓ છાત્રાલય ઉમેરોઊંડાવિધાપીઠ યુનિવર્સિટી, pipariya.

પ્રોટોકોલ કોઈ .: XXXXXXXX

સંમત INFORM

અભ્યાસમાં શીર્ષક: ઓબ્ઝર્વેશનલ અભ્યાસમાં નીચલા પેટનો અને નીચલા અંગ શસ્ત્રક્રિયા માટે કરોડરજ્જુ એનેસ્થેસિયાના એક સહાયક તરીકે dexmedetomidine અને clonidine સાથે Isobaric Ropivacaine 0.75% અસર સરખાવવા માટે.

StudyNumber:

વિષયની પ્રારંભિક: વિષયની નામ:

જન્મ / ઉંમર તારીખ:

આ વિષય ની સરનામું: _

લાયકાત:

વ્યવસાય: વિદ્યાર્થી / સ્વ રોજગારી / સેવા / હાઉસ-પત્ની / અન્ય:

(યોગ્ય નિશાની કરો)

વિષય વાર્ષિક આવક:

નામાંકન (ઓ) ની વિગતો:

નામાંકન નામ:

નામાંકન ની સરનામું:

વિષય સંબંધમાં:

બોક્સ (વિષય) પ્રારંભિક કૃપા કરીને

હું વાંચી અને ક આ જાણકારી શીટ સમજી છે તેની ખાતરી .... ઉપરના અભ્યાસમાં હના માટ અને પ્રશ્નો પૂછી તક મળી છે.

(૨) હું અભ્યાસમાં મારો સહયોગ સ્વૈચ્છિક છે અને હું મારા તબીબી સંભાળ વિના, કોઈ કારણ આપ્યા વગર, કોઈપણ સમયે પાછી ખેંચી મુક્ત છું કે કાનૂની અધિકારો અસર થઈ રહી છે કે જે સમજે છે.

હું કે જે ક્લિનિકલ ટ્રાયલ ઓફ પ્રાયોજક, અન્ય સમજવા

આ પ્રાયોજક વતી કામ, આ એથિક્સ સમિતિ અને નિયમનકારી સત્તાવાળાઓ વર્તમાન અભ્યાસ અને આગળ કોઈ બાબતમાં બંને મારા આરોગ્ય રેકોર્ડ જોવા માટે મારા પરવાનગી જરૂર નથી

પ્રોટોકોલ કોઈ .: XXXXXX

તે સંબંધમાં કરવામાં આવેલા થઈ શકે છે સંશોધન,

પણ હું ટ્રાયલ ખસી તો. હું આ ઍક્સેસ કરવા માટે સંમત. જો કે, હું મારી ઓળખ તૃતીય પક્ષો માટે રજૂ અથવા પ્રકાશિત કોઈપણ માહિતી જાહેર કરવામાં આવશે નહીં કે સમજવા.

હું માત્ર વૈજ્ઞાનિક હેતુ (ઓ) માટે છે, જેમ કે એક ઉપયોગ પૂરી પાડવામાં આ અભ્યાસ પરથી ઊભી થાય કે જે કોઈપણ માહિતી અથવા પરિણામો ઉપયોગ મર્યાદિત કરવા નથી સંમત

(V) હું ઉપર અભ્યાસમાં ભાગ લેવા માટે સંમત છો.

આ વિષય / LAR ની સહી (અથવા થંબ છાપ):

તારીખ: / /

સહી માતાનો નામ:

આ તપાસનીશ ના હસ્તાક્ષર:

તારીખ: / /

તપાસનીશ નામ અભ્યાસ:

આ સાક્ષી ની સહી

તારીખ: / _ /

આ સાક્ષી નામ:

પેશન્ટ માહિતી શીટ ની નકલ અને યોગ્ય જાણકાર ભરી સંમતિ ફોર્મ વિષય સોંપી દેવામાં અથવા તેના / તેણીના પરિચર આવશે.

ROPIVACAINE 3ML + DEX 5MCG

Sl.No.	Date	Age (years)	Sex	Height(cm)	Weight (kg)	ASA Grading	Sensory Block Onset	Motor block Onset(min)	INTRAOPERATIVE MONITORING																															
									PULSE (beats/min)											SYSTOLIC BP(mm of Hg)												DIASTOLIC BP(mm of Hg)											
									0	1	3	5	10	15	30	45	60	90	120	180	0	1	3	5	10	15	30	45	60	90	120	180	0	1	3	5	10	15	30	45	60	90	120	180
1	1/4/2015	45	M	168	64	I	5	10	96	102	99	96	93	90	88	87	85	83	81	83	134	130	126	124	122	120	122	118	116	118	122	118	86	84	80	80	79	78	78	76	74	76	78	
2	1/4/2015	26	F	172	68	II	4	12	86	92	89	87	85	83	81	79	77	75	74	75	114	110	106	102	103	104	102	101	100	99	102	99	70	70	66	68	66	64	68	64	64	66	68	66
3	4/4/2015	35	M	168	58	I	4	12	81	88	86	84	80	77	74	73	71	70	69	70	122	119	115	112	110	112	110	108	106	108	108	108	90	86	74	73	70	68	70	67	64	68	70	72
4	4/4/2015	28	F	166	70	I	5	10	102	109	105	101	99	96	94	91	89	86	85	86	114	110	108	106	104	103	104	102	105	103	106	103	72	70	70	68	66	70	64	66	67	60	62	64
5	4/9/2015	45	M	169	63	I	5	12	88	95	93	90	86	83	81	79	76	74	72	74	128	125	122	118	114	110	108	106	107	106	108	106	80	77	76	74	72	72	70	72	74	72	74	74
6	4/17/2015	45	M	165	72	I	5	11	98	105	101	98	95	93	91	90	88	87	86	87	130	128	126	122	120	118	118	116	113	114	116	114	84	81	78	78	78	76	74	74	72	70	72	74
7	4/20/2015	50	F	170	80	II	4	12	91	97	93	91	87	85	82	80	77	76	74	76	140	137	134	132	128	126	124	122	120	118	122	118	90	86	86	84	84	80	76	76	74	84	82	82
8	4/24/2015	50	M	166	65	I	5	13	84	91	87	82	79	76	74	73	71	70	69	70	118	114	112	110	110	108	106	104	104	106	108	106	76	74	72	74	70	66	64	68	64	64	66	68
9	4/24/2015	40	M	155	61	I	5	11	76	85	83	79	75	72	69	68	66	64	62	64	124	122	120	118	116	114	112	110	112	112	114	112	78	76	74	72	70	70	66	66	64	66	68	70
10	4/24/2015	21	M	154	74	I	5	12	100	107	103	99	96	93	91	88	86	84	83	84	136	134	132	130	128	126	124	122	118	116	114	116	88	85	84	82	80	77	76	74	72	74	76	78
11	4/27/2015	21	M	167	71	II	4	10	85	92	88	84	81	78	76	74	72	70	68	70	126	124	120	118	116	114	112	110	112	114	114	114	74	70	68	66	64	66	64	66	66	66	66	68
12	4/27/2015	50	M	170	68	I	4	12	80	88	84	79	75	72	70	68	66	64	63	64	116	114	112	110	108	106	104	102	104	106	108	106	84	82	80	78	76	77	72	70	72	74	74	74
13	5/5/2015	60	F	166	70	I	4	12	88	95	93	89	85	81	77	74	71	70	68	70	120	117	114	112	110	108	106	104	104	106	108	106	78	76	74	72	74	73	74	74	72	70	72	74
14	5/11/2015	50	F	156	66	I	5	10	93	101	97	90	87	83	81	80	78	76	75	76	132	128	125	124	119	118	116	114	112	114	115	114	84	78	78	76	74	74	72	74	73	74	74	76
15	5/11/2015	45	M	165	72	II	5	11	83	90	85	80	77	74	71	68	66	63	62	63	116	114	112	110	108	107	106	104	102	100	103	100	74	71	70	70	67	68	72	66	64	64	63	64
16	6/19/2015	30	M	170	64	I	4	12	79	87	83	80	76	73	71	67	64	62	60	62	122	119	118	116	112	110	108	107	106	105	106	105	74	73	71	70	68	66	68	66	64	66	68	68
17	6/19/2015	50	M	169	75	I	4	10	81	91	87	82	77	73	70	68	66	64	62	64	112	110	108	106	105	103	102	102	104	100	103	100	70	70	68	64	63	60	62	64	64	62	62	64
18	6/19/2015	25	M	166	67	I	5	11	97	105	102	98	94	91	88	85	83	82	80	82	116	113	112	110	107	104	102	100	104	106	104	106	77	74	73	70	70	64	63	60	66	68	70	72
19	6/23/2015	39	M	156	65	I	4	12	89	98	94	90	87	84	80	79	77	75	73	75	130	126	122	118	116	114	112	110	112	113	110	113	90	88	84	80	80	78	80	82	78	78	80	80
20	6/25/2015	60	M	167	71	I	5	11	77	86	78	75	73	71	69	67	64	62	60	62	126	122	119	116	113	112	110	109	108	106	104	106	84	82	80	78	76	74	73	72	72	70	70	72
21	7/1/2015	50	M	158	66	I	5	10	85	93	90	86	82	80	78	76	74	72	71	72	120	118	116	114	114	112	110	108	108	107	106	107	76	74	75	76	74	73	72	70	70	68	70	70
22	7/3/2015	31	M	154	58	I	4	12	92	100	96	91	87	83	80	78	76	74	73	74	136	134	132	128	124	120	117	116	114	112	110	112	88	85	83	82	80	78	76	74	72	72	74	74
23	7/21/2015	44	M	166	72	II	4	12	83	91	87	82	78	75	72	70	67	66	65	66	128	126	124	121	118	116	114	112	113	112	114	112	74	72	71	68	66	66	64	62	63	64	66	68
24	7/21/2015	59	M	167	78	I	4	11	77	85	82	78	74	71	69	66	65	64	62	64	130	126	124	122	120	118	116	114	114	112	113	112	86	84	84	81	80	78	72	72	74	70	70	72
25	7/22/2015	19	M	170	64	I	4	12	86	95	91	87	82	78	76	73	70	68	66	68	118	116	114	112	110	108	108	106	105	106	108	106	84	82	82	80	80	78	76	77	76	76	76	76
26	7/30/2015	52	M	152	71	II	5	10	103	110	106	102	99	96	93	90	88	87	85	87	136	134	132	130	128	126	124	122	120	118	120	118	90	89	86	84	83	84	82	80	80	76	77	78
27	9/4/2015	55	M	164	66	I	4	12	82	89	84	81	78	74	71	69	67	75	73	75	114	112	110	108	108	106	104	102	103	106	107	106	74	74	72	70	68	66	66	68	70	72	72	74
28	9/4/2015	42	M	150	76	I	5	12	94	102	98	93	89	85	82	80	77	75	75	75	128	125	122	120	118	115	112	110	112	110	108	110	80	78	76	74	72	70	66	64	66	66	64	66
29	9/8/2015	55	M	166	64	I	4	11	79	87	83	78	74	71	69	66	64	62	60	62	122	120	118	116	114	110	106	104	102	100	104	100	76	76	74	76	73	72	71	70	68	64	66	68
30	9/9/2015	37	M	168	70	I	5	11	85	93	88	84	81	77	74	72	70	69	68	70	132	130	128	124	118	116	114	113	112	114	112	114	86	84	80	82	80	82	80	78	76	73	74	72

ROPIVACAINE 3ML + DEX 5MCG

Sl.No.	SPO2												SEDATION SCORE												Level	Sensory block duration	Motor block duration	Total duration of analgesia	2 Segment regression		Post operative complicati
	0	1	3	5	10	15	30	45	60	90	120	180	0	1	3	5	10	15	30	45	60	90	120	180					Rescue	Analg	
1	98	98	98	98	99	98	97	98	98	98	98	99	1	1	1	2	2	2	2	2	2	2	2	1	T8	340	280	400	410	152	No
2	100	100	99	100	100	99	100	100	100	100	100	100	1	1	1	1	1	1	1	1	1	1	1	1	T8	360	302	415	425	156	No
3	99	99	100	99	99	99	99	100	100	99	98	99	1	1	1	1	2	2	2	2	2	2	2	1	T8	360	295	405	420	158	No
4	99	99	99	99	99	100	99	99	98	99	99	99	1	1	1	1	2	2	2	2	2	2	2	1	T8	355	296	415	420	155	No
5	97	97	98	98	97	98	97	97	97	97	98	97	1	1	1	2	2	2	2	2	2	2	2	2	T8	350	304	420	430	148	No
6	100	100	100	100	99	99	99	100	100	99	100	99	1	1	1	1	1	1	1	1	1	1	1	1	T8	330	286	410	426	138	No
7	98	98	97	98	98	99	98	98	98	98	98	98	1	1	1	2	2	2	2	2	2	2	1	1	T8	360	308	415	427	152	No
8	99	99	99	99	98	98	99	99	100	99	98	99	1	1	1	1	2	2	2	2	2	2	2	1	T8	350	302	418	429	143	No
9	100	100	99	100	100	99	100	100	100	100	100	99	1	1	1	1	2	2	2	2	2	2	2	2	T8	352	302	412	425	145	No
10	97	97	98	98	97	98	97	97	97	98	98	97	1	1	1	1	2	2	2	2	2	2	2	1	T8	347	300	416	428	143	No
11	99	99	99	98	98	98	99	99	98	99	98	98	1	1	1	1	1	1	1	1	1	1	1	1	T8	343	283	408	413	141	No
12	100	100	99	100	100	99	100	100	99	100	100	99	1	1	1	2	2	2	2	2	2	2	1	1	T8	349	292	412	420	147	No
13	100	100	100	99	99	100	99	100	100	99	100	99	1	1	1	1	2	2	2	2	2	2	2	1	T8	350	302	420	432	147	No
14	99	99	99	99	98	99	99	99	99	99	98	99	1	1	1	1	1	1	1	1	1	1	1	1	T8	360	297	416	429	156	No
15	99	99	99	99	98	99	99	99	98	98	98	98	1	1	1	2	2	2	2	2	2	2	1	1	T8	346	280	408	417	145	No
16	100	100	99	99	100	99	100	100	99	100	100	100	1	1	1	1	1	2	2	2	2	2	2	1	T8	348	290	415	424	147	No
17	99	99	99	98	98	99	99	99	98	98	98	99	1	1	1	2	2	2	2	2	2	2	2	2	T8	350	292	420	432	148	No
18	98	98	97	97	98	99	98	98	98	98	98	98	1	1	1	1	2	2	2	2	2	2	2	1	T8	350	286	406	417	150	No
19	97	97	98	98	97	97	97	97	96	97	98	97	1	1	1	1	1	2	2	2	2	2	2	1	T8	353	290	410	418	155	No
20	98	98	98	98	99	99	97	98	98	98	98	99	1	1	1	2	2	2	2	2	2	2	2	2	T8	355	290	416	429	158	No
21	100	100	100	99	100	99	100	100	99	99	100	99	1	1	1	1	1	1	1	1	1	1	1	1	T8	360	292	412	420	154	No
22	99	99	99	98	98	98	99	99	99	98	98	99	1	1	1	2	2	2	2	2	2	2	1	1	T8	340	282	406	418	141	No
23	100	100	99	100	100	99	100	100	99	99	100	100	1	1	1	2	2	2	2	2	2	2	2	2	T8	352	300	415	428	152	No
24	100	100	99	100	100	99	100	100	100	100	100	99	1	1	1	1	2	2	2	2	2	2	2	2	T8	350	290	412	422	149	No
25	99	99	99	99	98	99	99	99	100	99	98	99	1	1	1	1	1	1	1	1	1	1	1	1	T8	350	288	415	428	153	No
26	100	100	100	100	100	99	100	100	99	100	100	100	1	1	1	1	2	2	2	2	2	2	2	1	T8	356	300	420	428	155	No
27	99	99	99	99	98	98	99	99	99	99	98	99	1	1	1	2	2	2	2	2	2	2	2	2	T8	345	286	410	417	147	No
28	97	97	98	98	97	98	97	97	97	96	96	97	1	1	1	1	2	2	2	2	2	2	2	2	T8	340	288	406	421	141	No
29	99	99	99	98	98	99	99	99	99	98	98	98	1	1	1	1	1	1	1	1	1	1	1	1	T8	338	296	416	429	140	No
30	100	100	100	100	100	99	100	100	99	99	100	100	1	1	1	2	2	2	2	2	2	2	1	1	T8	353	292	410	422	152	No