University of Khartoum
The Graduate College
Postgraduate Medical and Health Studies Board

Analgesic Efficacy and Adverse Effects of Intrathecally Administered Neostigmine in Patients Submitted to Spinal Anaesthesia

By

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SUPERVISOR

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DEDICATION

♦ To my amazing parents

♦ To my wife, Dr. Belques, for being so supportive and understanding

♦ To my teachers, colleagues and friends for their help and inspiration
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I would like to thank all my patients for their acceptance and pleasant co-operation.
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<table>
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<tbody>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologist</td>
</tr>
<tr>
<td>ACh</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
</tr>
<tr>
<td>GA</td>
<td>General Anaesthesia</td>
</tr>
<tr>
<td>IT</td>
<td>Intrathecal</td>
</tr>
<tr>
<td>KTH</td>
<td>Khartoum Teaching Hospital</td>
</tr>
<tr>
<td>LA</td>
<td>Local anaesthetics</td>
</tr>
<tr>
<td>PDPH</td>
<td>Post dural puncture headache</td>
</tr>
<tr>
<td>SA</td>
<td>Spinal Anaesthesia</td>
</tr>
<tr>
<td>SC</td>
<td>Spinal Cord</td>
</tr>
<tr>
<td>SUH</td>
<td>Soba University Hospital</td>
</tr>
<tr>
<td>TNS</td>
<td>Transient Neurological Symptoms</td>
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<td>VAS</td>
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Background:

Spinal administration of neostigmine as a non-opioid analgesic appears to provide a potent, long lasting analgesia. The present study was designed to evaluate the effects of the addition of different doses of neostigmine on the characteristics of spinal anaesthesia using bupivacaine, and to assess their postoperative analgesic efficacy and safety in patients undergoing infra-umbilical surgery under spinal anaesthesia.

Methods:

In this prospective study, we studied sixty Sudanese patients, classified as class 1 and 2 according to the American society of anesthesiologist (ASA), in the age group 19 - 65 year old. They were scheduled for infra-umbilical surgery under spinal anaesthesia. Patients were randomly allocated to one of three groups (n=20 each): group one received intrathecal bupivacaine 15 mg, and group two received intrathecal bupivacaine 15 mg and neostigmine 50 µg, and group three received intrathecal bupivacaine 15 mg and neostigmine 100µg. The onset of anaesthesia, the duration of complete postoperative analgesia, the time to use of the first rescue analgesics, the overall 24-h VAS pain scores, and the incidence of adverse effects, if any, were recorded for 24-h post drug administration. Intraoperative and postoperative blood pressure, heart rate, and oxygen saturation, and total amount of analgesic consumed overall 24-h, were also recorded.

Results:

Onset of anaesthesia (level to pinprick at 5 and 10 minuets) was significantly earlier for group 2 and 3 patients compared with group 1 patients. Motor block (time to lift leg) was greatly prolonged for group 3
patients. There was a significant prolongation in the duration of absolute analgesia between different groups (p < 0.05). Group 3 patients, also showed a lower overall 24-h VAS pain score and prolonged time to first rescue analgesics. There was a dose dependent increase in the severity of nausea and vomiting with highest VAS nausea score in group 3 patients.

**Conclusion:**

The combination of 50 µg or 100 µg neostigmine with 15 mg of hyperbaric bupivacaine, given intrathecally, delayed postoperative pain for 4.7 – 6 h and lowered the number of rescue analgesics, in dose dependent manner. Because the better quality of analgesia was obtained with an increased (statistically significant differences) in incidence of untoward side effects, larger samples should be studied before this application can be routinely used clinically.
ملخص الأطروحه

خلفية وهدف الدراسة:

أظهرت معظم الدراسات أن استعمال النيوستيقمين (neostigmine) كعقار غير أفيوني في التخدير النصفي آدى إلى انخفاضا أكيراً في نتائج الألم

الهدف من هذه الدراسة هو تقييم تأثير جرعات مختلفة من عقار النيوستيقمين على خصائص التخدير النصفي، مضاءفة إلى المدخن الموضعي بوبيفاكين الثقيل (heavy bupivacaine)، وكذلك ملاحظة الفعالية والأمان في استخدامه كمسكن بعد العمليات الجراحية تحت السرة.

طريقة الدراسة:

أجريت هذه الدراسة المستقبلية لستون مريضاً (مربيضاً) سوداني الجنسية، من الدرجة الأولى والثانية لتخصص جمعية أخصائي التخدير الأمريكيه (Anesthesiologist) بفاعلية الصحية مابين عمر 21 - 65 سنة، حضروا لأداء عمليات جراحية باردة تحت تأثير التخدير النصفي.

تم اختيار وتصنيف المرضى عشوانياً إلى ثلاث مجموعات في كل منها 20 مريضاً، أعطيت المجموعة الأولى 15 ملم بوبيفاكين فقط وأضيف 50 و 100 ميكروجرام نيوستيقمين للمجموعة الثانية والثالثة بالتالي.

تمت مقارنة بداية تأثير المسكن، مدة المسكن، وقت طلب المريض لمسكن آخر ومعدل الشعور بالألم خلال ال24 ساعة التي تلت العملية. كذلك تمَّت مقارنة العلامات الحيوية للمريض (الضغط، معدل ضربات القلب والنفاس، معدل تشع الهد بالآكسجين) طوال فترة العملية وفي غرفة الافاقية، لمدة ساعتين بعد العملية. وقد تم تسجيل أي تأثيرات جانبية للعقار طوال فترة ال24 ساعة بعد العملية.

النتائج:

أدت هذه الإضافة إلى تحسن بداية تأثير المخدر الموضعي بوبيفاكين في المجموعة الثالثة مقارنة بالمجموعة الأولى. كذلك تم تسجيل زمن أطول لقدر المريض على بداية تحريك الأطراف ورفعها عن السرير فكانت أطول في المجموعة الثالثة والثانية مقارنة بالأولى.

في هذه الدراسة وجد أن استعمال عقار النيوستيقمين مع عقار الوبيفاكين الثقيل (0.5%) كان له تأثيراً إيجابياً في تأخير الشعور بالألم بعد العملية. كذلك تم تسجيل عدد أقل من المسكن الثاني، ديكلوفيناك (diclofenac)، الذي تم اعطاءه للمرضى بعد العملية طوال الشعور بالألم.
فقد كان الشعور بالغثيان والقيء هما أكثر المضاعفات حدوثًا، وتناولت شدتهما تناصباً طردياً مع زيادة جرعة عقار النيوستيقمين.

الخلاصة:

خلصت هذه الدراسة إلى أن استعمال جرعة مختلفة 50 و100 ميكروجرام من عقار النيوستيقمين، مع عقار البيوبيفاكن الثقيلة، أدى إلى تأخير الشعور بالألم (4.7 – 6 ساعات) وانخفاض في استعمال المسكنات بعد العملية، بصورة جيدة ومجدية إحصائيًا. ارتبطت شدة التأثيرات الجانبية بزيادة جرعة عقار النيوستيقمين، لذلك يجب إجراء دراسة أشمل وبجرعات أقل من تلك الموصى بها والتي استخدمت في هذه الدراسة.
Chapter 1
INTRODUCTION, LITERATURE REVIEW AND OBJECTIVES
INTRODUCTION

Acute pain is typically associated with a neuroendocrine stress response that is proportional to pain intensity. Moderate to severe acute postoperative pain, regardless of site, can affect every organ function and may adversely influence postoperative morbidity and mortality. The latter suggest that effective postoperative pain management is not only humane but also a very important aspect of postoperative care.\(^{(1)}\)

Intrathecal and epidural administration of opioids is commonly used in order to provide postoperative analgesia without sensory or motor blockade. Unfortunately, the use of neuraxial opioids is often associated with adverse effects, especially delayed respiratory depression. In an attempt to develop non-opioid analgesics with fewer adverse effects, the activity of other neurotransmitters that participate in modulation of pain processing in the spinal cord, including acetylcholine (ACh) has been examined.\(^{(2)(3)}\)

Recently, the spinal cholinergic system has gained new interest as a pharmacological target to accomplish efficient antinociception without the limitation of opioid-induced side effects. Thereby cholinergic agonists and acetylcholinesterase inhibitors were investigated with respect to their specific antinociceptive activity, to any potential side effects, and regard to any potential toxicity after their spinal administration.\(^{(4)(5)}\) In addition, several interactions with different pain modulating systems like the opioid-and \(\alpha_2\)-adrenergic receptors have been elucidated.\(^{(6)}\)

It was demonstrated that ACh is present in the intrinsic spinal neurons, in descending supraspinal fibers as well as in primary afferent fibers. Thus, ACh is considered one of the major neurotransmitters in pain modulation.\(^{(7)}\) Subsequently, it was shown in many studies that the spinal delivery of cholinergic agonists will result in analgesia, which is mediated through the
interaction with spinal noradrenergic-cholinergic neurons corresponding with
neurons in lamina 1 and 2 of spinal dorsal horn. (8)

This analgesic action appears to be related to muscarinic receptors rather than
nicotinic receptors activation. Thereby M₁ and M₂ receptors are
suggested to be mainly involved in the spinal antinociception. However, these
receptors will be also activated by inhibition of the breakdown of endogenous
acetylcholinesterase. In addition, the spinal delivery of neostigmine was
demonstrated to result in a dose-dependent analgesia in different species,
including men. In the case of neostigmine, its analgesic potency is related to
activation of the ACh release, and thus will be enhanced in specific pain states
with tonic release of ACh like neuropathic pain or inflammatory pain
disorders. (9)

Before its spinal use in humans, numerous animal studies in different
species were performed, analyzing its spinal pharmacology and toxicity. After
the assessment of its safety in the studies, intrathecal administration of
neostigmine in healthy volunteers was performed. Thereby it was shown that
typical non-dangerous, adverse events would be nausea, vomiting, sedation,
slight motor weakness, increased heart rate, and blood pressure. However, all
side effects were dependent on dose, method of administration (needle size)
and baricity of the solution injected. (10)

Dose of 50 to 100 micrograms (µg) of spinally administered
neostigmine appeared to be the optimal analgesic dose providing analgesia
comparable to morphine, lasting 24 hours. (11)

Spinal administration of neostigmine as a non-opioid analgesic appears
to provide a potent, long lasting analgesia. However, its clinical feasibility has
still to be assessed with special regards to its side effects, mainly nausea and
vomiting. Promising perspectives of spinally administered neostigmine will
be its use as an analgesic in distinct pain states such as Neuropathic or cancer
related pain syndrome.
1. SPINAL ANAESTHESIA

1.1 INTRODUCTION:

Spinal, caudal and epidural blocks (neuraxial anaesthesia) were first used for surgical procedures at the turn of last century when August Biers credited with administering the first spinal anaesthesia in 1898; he used 3ml of 0.5 cocaine intrathecally. (12)

These central blocks were widely used prior to the 1940s until increasing reports of permanent neurologic injury appeared. (13)

Publication of a large-scale epidemiological study in the 1950s showed that complications were rare when these blocks were performed skillfully with attention to asepsis and newer, safer local anaesthetics were used. (14)(15)

Sir Robert Macintosh was a giant of our specialty (1897-1989). As an author, his books (particularly *Local Anesthesia: Brachial Plexus*, and *Lumbar Puncture and Spinal Anesthesia*) were very influential. Resurgence in the use of central blocks ensued, and today, they are once again widely used in clinical practice. (16)

Spinal anaesthesia is easy to perform and has the potential to provide excellent operating conditions for surgery below umbilicus. If the anaesthetist has an adequate knowledge of the relevant anatomy, physiology, and pharmacology, safe and satisfactory anaesthesia can easily be obtained to the mutual satisfaction of the patient, surgeon and anaesthetist.

Spinal anaesthesia is induced by injecting a small amount of local anaesthetic (LA) into the cerebro-spinal fluid (CSF). The injection is usually made in the lumbar spine below the level at which spinal cord ends (L2).
1.2 ADVANTAGES OF SPINAL ANAESTHESIA:

- **Cost:** Anaesthetic drugs and gases are costly and the latter often difficult to transport. The costs associated with spinal anaesthesia are minimal.\(^{(17)}\)

- **Patient satisfaction:** If a spinal anaesthetic and the ensuing surgery are performed skilfully, the majority of patients is very happy with the technique and appreciates the rapid recovery and absence of side effects.

- **Respiratory disease:** Spinal anaesthesia produces few adverse effects on the respiratory system as long as unduly high blocks are avoided. Reduction of parental opiate requirements may decrease the incidence of aspiration pneumonia and hypoventilation.\(^{(18)}\)

- **Patent airway:** As control of the airway is not compromised, there is a reduced risk of airway obstruction or the aspiration of gastric contents. This advantage may be lost if too much sedation is given.

- **Diabetic patients:** There is little risk of unrecognized hypoglycaemia in an awake patient. Diabetic patients can usually return to their normal food and insulin regime soon after surgery as they experience less sedation, nausea and vomiting.\(^{(19)}\)

- **Muscle relaxation:** Spinal anaesthesia provides excellent muscle relaxation for lower abdominal and lower limb surgery.

- **Bleeding:** Blood loss during operation is less than when the same operation is done under general anaesthesia. This is because of a fall in blood pressure and heart rate and improved venous drainage with a resultant decrease in oozing.

- **Splanchnic blood flow:** Because it increases blood flow to the gut, spinal anaesthesia may reduce the incidence of anastomotic dehiscence.

- **Visceral tone:** The bowel is contracted during spinal anaesthesia and sphincters are relaxed although peristalsis continues. Normal gut function rapidly returns following surgery.
- **Coagulation**: Post-operative deep vein thromboses and pulmonary emboli are less common following spinal anaesthesia. (20)

- **Cardiac disease**: SA may reduce the incidence of cardiac complications in high risk patients. Decreasing the neuroendocrine stress response to surgery, patients with coronary artery disease may show less perioperative ischemia and reduce morbidity and mortality.

- **Cesarean section**: It is most commonly performed under spinal or epidural anaesthesia. It allows a mother to remain awake and experience the birth of her child. Large population studies in Great Britain and in the USA have shown that regional anaesthesia is associated with less maternal morbidity and mortality than is GA, which may be largely due to reducing the incidence of pulmonary aspiration and failed intubation. (21)

### 1.3 DISADVANTAGES OF SPINAL ANAESTHESIA:

SA techniques have proved to be extremely safe when managed well; however, there is still a risk for complications. Adverse reactions and complications range from self-limited back soreness to debilitating permanent neurologic deficits and even death.

The practitioner must therefore have a good understanding of the anatomy involved, be thoroughly familiar with the pharmacology and toxic dosages of the agents employed, diligently employ sterile technique and quickly treat physiologic derangement.

Some patients are not psychologically suited to be awake, even if sedated, during an operation. They should be identified during the preoperative assessment. Likewise, some surgeons find it very stressful to operate on conscious patients.

Even if a long-acting local anaesthetic is used, a spinal anaesthesia is not suitable for surgery lasting longer than approximately 2 hours. Patients find lying on an operating table for long periods uncomfortable. If an operation unexpectedly lasts longer than this, it may be necessary to convert
to a general anaesthetic or supplement the anaesthetic with intravenous ketamine or with a propofol infusion if that drug is available.

1.4 ANATOMY OF SPINAL CORD

1.4.1 The vertebral column:

The spinal cord (SC) and its nerve roots lie within the central bony canal of the vertebral column (VC) which is made up of 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal. With some notable exceptions, most vertebrae have similar features: a vertebral body anteriorly, two pedicles laterally, and two laminae posteriorly. Each has a midline spinous process that arises between the laminae and two transverse processes that arise laterally at the junction of the lamina and pedicle. These processes serve as attachments for ligaments and muscles. (22)

The first cervical vertebra, the atlas, lacks a body and has unique articulations with the base of the skull and the second vertebra. The later, also called the axis, consequently has atypical articulating surfaces. Sacral vertebrae normally fuse into one large bone, the sacrum. The lamina of S5 and all or parts of S4 normally don’t fuse, leaving a caudal opening to the spinal canal, the sacral hiatus. Coccygeal vertebrae are small rudimentary structures that also fuse.

Ligamentous elements provide structural support and together with supporting muscles help to maintain the unique double C-shape of the SC. Ventrally, the vertebral bodies and intervertebral disks are connected and supported by the anterior and posterior longitudinal ligaments. Dorsally, the ligamentum flavum, interspinous, and supraspinous ligament provide additional stability.

1.4.2 The spinal cord:

The spinal canal contains the SC with its coverings (meninges), fatty tissue, and a venous plexus. The meninges are composed of three layers: the
pia mater, arachnoid and the durra mater. The pia mater is closely adherent to
the SC. CSF is contained between the pia and arachnoid maters in the
subarachnoid space. The spinal subdural space is generally a poorly
demarcated, potential space. The epidural space is a better defined potential
space within the SC that is bounded by the dura and the ligamentum flavum.

The SC normally extends to the level of L₁ in adults and L₃ in children
but moves up as they grow older. The anterior and posterior nerve roots at
each spinal level join one another and exit the intervertebral foramina forming
spinal nerves from C₁ to S₄.

Because the SC normally ends at L₁, lower nerve roots must travel an
increasing distance (within the lumbar and sacral subarachnoid and epidural
spaces) from the SC to the intervertebral foramina. These lower spinal nerves
form the cauda equina, which is floating in the dural sac below L₁ and tend
to be pushed away (rather than pierced) by an advancing needle.

A dural sheath invests most nerve roots for a small distance even after
they exit the SC.

The blood supply to SC and nerve roots is derived from a single
anterior spinal artery and paired posterior spinal arteries. The anterior
spinal artery is formed from the vertebral artery at the base of the skull. It
supplies the anterior two-thirds of the cord, whereas the two posterior spinal
arteries supply the posterior one-third. They arise from the inferior cerebellar
arteries. The anterior and posterior spinal arteries receive additional blood
flow from the intercostal arteries in the thorax and the lumbar arteries in the
abdomen. One of these radicular arteries is typically large, the artery of
Adamkiewicz, arising from the aorta.

1.4.3 Surface anatomy:

Spinous processes are generally palpable and help to define the midline of
the back. Some useful surface markings:
- The spinous processes of the cervical and lumbar spines are nearly horizontal whereas those in the thoracic spine slant in a caudal direction and can overlap significantly.
  - The vertebral prominence (spine of C7) is easily palpable.
  - The tip of the spine T3 is opposite the roots of the spines scapula, with arms at the sides of the body.
  - The tip of the spine T7 is opposite the inferior angle of the scapula, with arms to the sides.
  - The highest points of the iliac crests are usually on a line crossing the spine of L4 or the L4-L5 interspace.
  - The dimples overlying the posterior superior iliac spines are on a line crossing the second, posterior sacral foramina and at this level the dural sac in the adult usually ends.
  - The lower end of the SC terminates at the level of the upper border of the body of L2.

1.5 PHYSIOLOGY OF SPINAL CORD

The principal site of action of neuraxial blockade is the nerve root. Local anaesthetic (LA) is injected into CSF and bathes the nerve root in the subarachnoid space. The CSF concentration of LA is thought to have minimal effects on the SC itself. Direct injection of LA into CSF, however, allows a relatively small quantity and volume of LA to a chief high level of sensory and motor blockade. Blockade of neural transmission in the posterior nerve root fibers interrupts somatic and visceral sensation while blockade of anterior nerve root fibers prevents efferent motor and autonomic outflow. (24)

1.5.1 Somatic blockade:

By interrupting the transmission of painful stimuli (both somatic and visceral) and abolishing skeletal muscle tone, spinal blocks can provide excellent operating conditions. The effect of LA on nerve fibers varies according to the size of the nerve fiber, whether or not it is myelinated, and
the concentration achieved and the duration of contact. Smaller and myelinated fibers are generally more easily blocked than larger unmyelinated ones. Table 1 contains the most commonly used classification systems for nerve fibers. \(^{(25)}\)

In general, the concentration of LA decreases with increasing distance from the level of injection as does the concentration gradients. **Differential blockade** typically results in sympathetic blockade that may be two segments higher than the sensory block, which in turn is two segments higher than motor blockade. \(^{(26)}\)

**Table 1**: classification of peripheral nerves according to fiber size and physiologic properties:

<table>
<thead>
<tr>
<th>Fiber Class</th>
<th>Sub-class</th>
<th>Myelin Diameter (µ)</th>
<th>Conduction Velocity (m/s)</th>
<th>Location Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>α</td>
<td>+ 6-22</td>
<td>30-120</td>
<td>Afferent to and efferent from muscles and joints Motor, proprioception</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>+ 6-22</td>
<td>30-120</td>
<td>Afferent to and efferent from muscles and joints Motor, proprioception</td>
</tr>
<tr>
<td></td>
<td>γ</td>
<td>+ 3-6</td>
<td>15-35</td>
<td>Efferent to muscle spindles Muscle tone</td>
</tr>
<tr>
<td></td>
<td>δ</td>
<td>+ 1-4</td>
<td>5-25</td>
<td>Afferent sensory nerve Pain, temperature, touch</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>&lt;3</td>
<td>3-15</td>
<td>Preganglionic sympathetic Various autonomic functions</td>
</tr>
<tr>
<td>C</td>
<td>-</td>
<td>0.3-1.3</td>
<td>0.7-1.3</td>
<td>Postganglionic sympathetic Various autonomic functions</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td>Afferent sensory nerves Pain, temperature, touch</td>
</tr>
</tbody>
</table>
1.5.2 Autonomic blockade:

Interruption of efferent autonomic transmission at the spinal nerve roots can produce sympathetic and some parasympathetic blockade. Sympathetic outflow from SC may be described as thoracolumbar, while parasympathetic outflow is craniosacral. Neuraxial blocks therefore primarily result in varying degrees of sympathetic blockade and physiologic responses, resulting from decreased sympathetic tone and/or unopposed parasympathetic tone.

- **Cardiovascular manifestations:**

  Spinal anaesthesia typically produces variable decrease in BP that may be accompanied by a decrease in heart rate and cardiac contractility. These effects are generally proportional to the degree (level) of the sympathectomy. Vasomotor tone is primarily determined by sympathetic fibers arising from T5 to L1, innervating arterial and venous smooth muscle. Blocking these nerves causes vasodilatation of the venous capacitance vessels, pooling of blood, and decreased preload to the heart; in some instances, arterial vasodilatation may also decrease SVR. The effects of arterial vasodilatation may be minimized by compensatory vasoconstriction above the level of the blockade. A high sympathetic block not only prevents compensatory vasoconstriction but also blocks the sympathetic cardiac accelerator fibers that arise at T1-T4.

  Profound hypotension may result from vasodilatation combined with bradycardia and decreased contractility. These effects are exaggerated if venous return is further compromised by a head-up position or from the weight of a gravid uterus. Unopposed vagal tone in some persons may explain cardiac arrest with SA. (27)

  Deleterious cardiovascular effects should be anticipated and steps undertaken to minimize the degree of hypotension.

- **Pulmonary manifestations:**

  SA to mid-thorax levels have little effect on pulmonary function in patients without pre-existing disease (drugs for sedation may have a greater effect).
The adverse impact of high blocks on active exhalation suggests caution when using SA in patients with COPD or those who rely on accessory muscles of respiration to maintain adequate ventilation.

Patients with high spinal may complain of dyspnea (loss of ability to feel chest movement while breathing, which is usually adequately treated by reassurance). A normal speaking voice, suggests ventilation is normal (faint gasping whisper with an excessively high block).

- **Gastrointestinal manifestations:**

  Sympathetic outflow originates at the T₅ - L₁ level. SA induced sympathectomy allows vagal tone dominance and results in a small, contracted gut with active peristalsis that can provide excellent operative conditions.

  Nausea is a common complication of SA (cause is unknown but often associated with; (1)blocks higher than T₅; (2)hypotension; (3)opioid administration; (4)traction on nerve endings and plexuses, especially via vagus; (5)psychological factors; (6)hypoxia; (7)presence of bile in stomach due to relaxation of pyloric and bile-duct sphincters). Treatment of nausea and vomiting consists in attending to the hypotension and hypoxia, if present; i.v. atropine; oxygen supplementation; deep breathing through the mouth; reassurance and attention to general comfort; antiemetics supplementation; i.v. anaesthesia with thiopentone and nitrous oxide-oxygen, or a volatile agent, if the condition persists or if the surgeon's work is being affected- full general anaesthesia.

- **Hepatic manifestations:**

  There are no specific effects of significance. Hepatic blood flow will decrease with reductions in mean arterial pressure from any anaesthetic technique. For intra-abdominal surgery the decrease in hepatic perfusion is more related to surgical manipulation than anaesthetic technique. Liver disease may interfere with the metabolism of LA drugs.
- **Urinary tract manifestations:**
  Renal blood flow is maintained through autoregulation, and there is little clinical effect upon renal function from SA. \(^{(30)}\)

  SA at the lumbar and sacral levels blocks both sympathetic and parasympathetic control of bladder function. Loss of autonomic bladder control results in urinary retention. If no urinary catheter is anticipated perioperatively, it is prudent to use shortest acting and least a moment of drug necessary for the surgical procedure and limit the amount of i.v. fluid administration (if possible).

- **Metabolic and endocrine manifestations:**
  Spinal blockade can partially suppress (during major invasive surgery) or a totally block (during lower extremity surgery) the neuroendocrine response which stimulated by the surgical trauma. A T\(_{11}\) block can block adrenal pathways and blunt hyperglycemia. By reducing catecholamine release, SA may decrease perioperative arrhythmias and possibly reduce the incidence of ischemia.

### 1.6 INDICATIONS FOR SPINAL ANAESTHESIA:

These vary greatly with different surgeons and anaesthetists. SA is best reserved for operations below the umbilicus e.g. hernia repairs, gynecological and urological operations and any operation on the perineum or genitalia. All operations on the leg are possible, but an amputation, though painless, may be unpleasant experience for an awake patient. In this situation it may be appropriate to combine the spinal with a light GA.

SA is particularly suitable for older patients and those with systemic diseases such as respiratory disease, hepatic, renal, and endocrine such as diabetes. \(^{(31)}\)

Useful when **muscle relaxants** are contra-indicated, or when it is thought advantageous to preserve **spontaneous respiration**. Patients with
chronic respiratory disease often do well with central neural blockade as tracheal intubation may be avoided.

Some patients fear loss of consciousness and prefer to remain awake. Acute cases, including obstetric patients, with a full stomach are of less risk of inhalation of stomach contents under spinal than with GA.\textsuperscript{(32)} There are definite advantages for both mother and baby in using spinal anaesthesia for caesarean section. However, special considerations apply to managing spinal anaesthesia in pregnant patients and it is best to become experienced in its use in the non-pregnant patient before using it for obstetrics. Some patients with compromised hepatorenal function may do well with central neural blockade. Skilled workers may meet fewer difficulties with SA than with GA in the morbidly obese patient. It is suitable for managing patients with trauma if they have been adequately resuscitated and are not hypovolaemic.\textsuperscript{(33)}

\section*{1.7 CONTRAINDICATIONS FOR SPINAL ANAESTHESIA:}

Most of the contra-indications to spinal anaesthesia apply equally to other forms of regional anaesthesia. These include:

\begin{itemize}
  \item **Inadequate resuscitation drugs and equipment:** No regional anaesthetic technique should be attempted if drugs and equipment for resuscitation are not immediately to hand.
  \item **Clotting disorders:** If bleeding occurs into the epidural space because the spinal needle has punctured an epidural vein, a haematoma could form and compress the spinal cord. Patients with a low platelet count or receiving anticoagulant drugs such as heparin or warfarin are at risk. Remember that patients with liver disease may have abnormal clotting profiles whilst low platelet counts as well as abnormal clotting can occur in pre-eclampsia.
  \item **Hypovolaemia:** If patients are hypovolaemic from whatever cause e.g. bleeding, dehydration due to vomiting, diarrhoea or bowel obstruction,
patients must be adequately rehydrated or resuscitated before spinal anaesthesia or they will become very hypotensive.

- **Patient refusal:** Patients may be understandably apprehensive and initially state a preference for general anaesthesia, but if the advantages of spinal anaesthesia are explained they may then agree to the procedure and be pleasantly surprised at the outcome. If, despite adequate explanation, the patient still refuses spinal anaesthesia, their wishes should be respected. Likewise, mentally handicapped patients and those with psychiatric problems need careful pre-operative assessment.

- **Children:** Although spinal anaesthesia has been successfully performed on children, this is a highly specialised technique best left to experienced paediatric anaesthetists. (34)

- **Sepsis:** Infection on the back near the site of lumbar puncture let infection be introduced into the epidural or intrathecal space.

- **Septicemia:** If a patient is septicemic, they are at increased risk of developing a spinal abscess. Epidural abscesses can, however, appear spontaneously in patients who have not had spinal/epidural injections especially if they are immuno-deficient: e.g. patients with AIDS, tuberculosis, and diabetes.

- **An anatomical deformity of the patient's back:** This is a relative contraindication, as it will probably only serve to make the dural puncture more difficult.

- **Neurological disease:** The advantages and disadvantages of spinal anaesthesia in the presence of neurological disease need careful assessment. Any worsening of the disease post-operatively may be blamed erroneously on the spinal anaesthetic. Raised intracranial pressure, however, is an absolute contra-indication as a dural puncture may precipitate coning of the brain stem.

Absolute, Relative and controversial contraindications are also listed in table 2.
### Table 2: contraindications to neuraxial blockade:

- **Absolute**
  - Infection at the site of injection
  - Patient refusal
  - Coagulopathy or other bleeding diathesis
  - Severe hypovolaemia
  - Increased intracranial pressure
  - Severe aortic stenosis
  - Severe mitral stenosis

- **Relative**
  - Sepsis
  - Uncooperative patient
  - Preexisting neurological deficit
  - Stenotic valvular heart disease
  - Severe spinal deformity

- **Controversial**
  - Prior back surgery at the site of injection
  - Inability to communicate with patient
  - Complicated surgery
    - Prolonged operation
    - Major blood loss
    - Maneuvers that compromise respiration.

### 1.8 FACTORS INFLUENCING LEVEL OF BLOCK:

A number of factors affect the spread of the injected local anaesthetic solution within the CSF and the ultimate extent of the block obtained.

Among these are:
the baricity of the local anaesthetic solution,
- the position of the patient,
- the concentration and volume injected,
- the level of injection,
- the speed of injection, and
- Other factors: age, CSF, curvature of the spine, intra-abdominal pressure, needle direction, patient height, and pregnancy.

Migration of local anaesthetic cephalad in CSF depends on its specific gravity relative to CSF (baricity). CSF has a specific gravity of 1.003-1.008. The specific gravity of the local anaesthetic solution can be altered by the addition of dextrose. Concentrations of 7.5% dextrose make the local anaesthetic hyperbaric (heavy) relative to CSF and also reduce the rate at which it diffuses and mixes with the CSF.(35) Isobaric and hyperbaric solutions both produce reliable blocks. Injecting hyperbaric solutions and then altering the patient's position probably produces the most controllable blocks.

If a patient is kept sitting for several minutes after the injection of a small volume of a hyperbaric solution of local anaesthetic, a classical "saddle block" affecting only the sacral nerve roots will result. (36)

The quantity of local anaesthetic (in milligrams) injected will determine the quality of the block obtained whilst its extent will also be determined by the volume in which it is injected. Large volumes of concentrated solutions will, thus, produce dense blockade over a large area. As spinal anaesthetics are generally only injected in the lumbar region, the extent of the block is influenced more by the volume and concentration injected and the position of the patient than the actual interspace at which the injection occurs.

The speed of injection has a slight effect on the eventual extent of the block. Slow injections result in a more predictable spread while rapid injections produce eddy currents within the CSF and a somewhat less predictable outcome. (37)
Finally, increased abdominal pressure from whatever cause (pregnancy, ascites etc.) can lead to engorgement of the epidural veins, compression of the dura and hence a reduction in the volume of the CSF. A given quantity of local anaesthetic injected into the CSF might then be expected to produce a more extensive block.\(^{(38)}\)

### 1.9 SPINAL ANAESTHETIC AGENTS:

Many local anaesthetics have been used for SA in the past, but only a few currently in uses (procaine 10\%, bupivacaine 0.5-0.7.5\%, tetracaine1\%, lidocaine 5\%, and robiavacaine 0.2-1\%). Only preservative-free local anaesthetics are used.\(^{(39)}\)

Addition of vasoconstrictors\(^{(40)}\) (\(\alpha\)- adrenergic agonists) and opioids\(^{(41)}\) greatly enhances the quality of SA vasoconstrictors include epinephrine (0.1-0.2mg) and phenylephrine (1-2mg). Both agents appear to decrease the uptake and clearance of local anaesthetics from CSF and may have weak analgesic properties.\(^{(42)}\)

Clonidine (\(\alpha_2\)-adrenergic agonist) provides dose-dependent analgesia and side effects of hypotension, bradycardia, and sedation, but not respiratory depression or pruritus.\(^{(43)}\)\(^{(44)}\)\(^{(45)}\) Acetylcholinesterase (e.g. neostigmine) also has spinal analgesic properties.\(^{(46)}\)

### 1.10 COMPLICATIONS OF SPINAL ANAESTHESIA:

The complications of SA range from the bother some to the crippling and life-threatening. Broadly, the complications can be thought of as those resulting from the medication introduced or the needle used. Backache, headache, nerve injury, vascular injury, and infection can result from the procedure needle. Medications can result in excessively high blockade, systemic toxicity, local toxicity (nerve injury) or infection. Ischemic injury may result from combination of factors. Cardiac arrest can occur with SA.\(^{(47)}\)
- **Backache:**

  It usually benign and self-limited, although it may last for a number of weeks, it may also be an important clinical sign of the much more serious complications, such as epidural haematoma and abscess. A localized inflammatory response with or without reflex muscle spasm may be responsible.

- **Headache:**

  The first successful spinal anaesthetic by August Bier (1898) was accompanied by a classic description of post-dural puncture headache (PDPH). Any breach of the dura may result in a PDPH. Typically the headache is **bilateral**, frontal or retro-orbital, occipital and extending into the neck. It may be throbbing or constant and associated with photophobia and nausea. The hallmark of PDPH is its association with body position, **aggravated** by sitting or standing and **relieved** or lessened by lying down flat. The **onset** is usually 12-72 hours following the procedure; however, it may be seen sooner. Untreated, the pain may last weeks, and in rare instances has required surgical repair.\(^{(48)}\)

  PDPH is believed to result from decreased intracranial pressure as CSF leaks from the dural defect at a greater rate than it is being produced. Recent data support this empiric mechanism of CSF loss causing PDPH, as MRI correlates CSF loss with PDPH.\(^{(49)}\) The incidence is related to needle size, needle type and patient population. The greater the needle is the greater the incidence of PDPH.\(^{(50)}\) Cutting point needles are associated a higher incidence of PDPH than pencil point needles of the same gauge. **Factors** that increase the risk of PDPH include young age, female sex, and pregnancy.

  Current non-invasive **treatments** (recumbent positioning, bed rest, fluids, analgesics, caffeine) only temporize the discomfort.\(^{(51)}\) Epidural blood patch is a very effective treatment for PDPH. It involves injecting 15-20 ml of autologous blood into the epidural space at or one interspace below the level of the dural puncture. It is believed to stop further leakage of CSF by either
mass effect or coagulation. Approximately 90% of patients will respond to a single blood patch, and 90% of initial non-responders will get relief from a second injection. Epidural patching with non blood substances (e.g. saline or colloid) are ineffective for prolonged relieve. Clinical strategies have focused on prophylactically reducing loss after dural puncture.

- **Urinary retention:**

  As the sacral autonomic fibers are among the last to recover following a spinal anaesthetic, urinary retention may occur. If fluid pre-loading has been excessive, a painful distended bladder may result and the patient may need to be catheterized.

- **Transient neurological symptoms:**

  First described in 1993, transient neurological symptoms (TNS) is characterized by back pain radiating to the legs without sensory or motor deficit, occurring after the resolution of spinal block and resolving spontaneously within several days. It is most commonly associated with hyperbaric lidocaine, but also been reported with others. It is highest among outpatients (early ambulation) after surgery in the lithotomy position.

  The pathogenesis of TNS is unclear and controversy exist as to whether it represents neurotoxicity (a mild form of the cauda equina syndrome), or myofacial pain resulting from musculoskeletal strain.

- **Cardiac arrest during spinal anaesthesia:**

  Examination of data from the American Society of anesthesiologist Close Claim project identified several cases of cardiac arrest during SA. A analysis indicate that the administration of sedation to produce a sleep-like state, with unrecognized hypoventilation (hypoxia) and lack of early administration of epinephrine were common patterns of management in cases of cardiac arrest.

  Large surveillance studies typically observed incidences of hypotension around (33%) and bradycardia around (13%). Prophylactic
volume expansion is recommended, as is early vagolytic (atropine) treatment of bradycardia followed by ephedrine and epinephrine if necessary.

- **Permanent neurological complications:**

  They are extremely rare. Many of those that have been reported were due to the injection of **inappropriate drugs** or **chemicals** into the CSF producing meningitis, arachnoiditis, transverse myelitis or the cauda equina syndrome with varying patterns of neurological impairment and sphincter disturbances.\(^{(57)}\)(\(^{(58)}\)) Damage to an epidural vein can lead to the formation of an epidural haematoma that compresses the spinal cord. This is most unlikely in a patient with a normal clotting profile. If inadequate sterile precautions are taken, **bacterial meningitis** or an epidural abscess may result although it is thought that most such **abscesses** are caused by the spread of infection in the blood.\(^{(59)}\)(\(^{(60)}\)) Finally, permanent paralysis can occur due to the "anterior spinal artery syndrome". This is most likely to affect elderly patients who are subjected to prolonged periods of hypotension and may result in permanent paralysis of the lower limbs.

- **Spinal or epidural haematoma:**

  The incidence of such haematomas has been estimated to be about 1:150,000 for epidural blocks and 1:220,000 for spinal anaesthetics. The onset of symptoms is typically more sudden onset compared with epidural abscess. Symptoms include sharp back and leg pain with a progression to numbness and motor weakness and/or sphincter dysfunction. Diagnosis and surgical decompression within 8-12 hrs of the onset of symptoms results in a good outcome.\(^{(61)}\)

  Spinal haematoma carries with it a rare but well-recognized risk of cord damage and paralysis or permanent anaesthesia. Abnormal clotting profiles either secondary to disease or pharmacologic therapies, hepatic cirrhosis, chronic renal failure, and spinabifida occulta, were reported risk factors.\(^{(62)}\)(\(^{(63)}\)(\(^{(64)}\))
Cranial subdural haematomas have occurred after lumbar puncture (L.P) in association with cerebral aneurysm, brain tumour, recent accident and meningovascular syphilis. It is postulated that the haemorrhage is caused by a sudden decrease in intracranial pressure consequent to the loss CSF at the L.P site. Sudden caudal shift of the brain may cause traction on the arachnoid matter and/or venous structures and may lead to bleeding from ruptured vessels.\(^{(65)}\)
2. SPINAL CORD PHYSIOLOGY AND PHARMACOLOGY OF PAIN

Normal pain perception depends on specialized neurons that function as receptors, detecting the stimulus, and then transduction, and conducting it into the CNS. Sensation is often described as either protopathic (noxious) or epicritic (non-noxious). **Non-noxious sensation** (light touch, pressure, proprioception, and temperature discrimination) is characterized by low-threshold receptors and generally conducted by large myelinated nerve fibers. In contrast, **noxious sensation** (pain) is subserved by high-threshold receptors and conducted by smaller, lightly myelinated (A\(\delta\)) and unmyelinated (C) fibers.

2.1 DEFINITION AND CLASSIFICATION OF PAIN:

**Pain** is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

The term nociception is used only to describe the neural response to traumatic or noxious stimuli.

Pain is **classified** according to pathophysiology, (e.g. nociceptive or neuropathic pain), etiology (e.g. postoperative or cancer pain), or the affected area (e.g. headache or low back pain). However, it is clinically useful to divide pain into one of two categories: (1) acute pain, which may be primarily due to nociception, and (2) chronic pain, which may be due to nociception but in which psychological and behavioral factors often play a major role. **Nociceptive pain** is due to activation or sensitization of peripheral nociceptors, specialized receptors that transduce noxious stimuli. **Neuropathic pain** is the result of injury or acquired abnormality of peripheral or central structures.
Acute pain can be defined as that which is caused by noxious stimulation due to injury, a disease process, or an abnormal function of muscle or viscera. Four physiological processes are involved: transduction, transmission, modulation, and perception. This type of pain is typically associated with a neuroendocrine stress that is proportional to intensity. Two types of acute (nociceptive) pain;

Somatic and visceral are differentiated based on origin and feature: (1) somatic pain, which can be further classified as superficial or deep, (2) visceral pain, this form of acute pain is due to a disease process or abnormal function of an internal organ or its covering.

2.2 ANATOMY OF NOCICEPTION

2.2.1 Pain pathways:

Pain is conducted along neuron pathways that transmit noxious stimuli from the periphery to the cerebral cortex. Primary afferent neurons are located in dorsal root ganglia, which lie in the vertebral foramina at each SC level. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates and the other into the dorsal horn of the SC. In the dorsal horn, the primary afferent neuron synapses with a second-order neurons whose axon cross the midline and ascend in the contralateral spinothalamic tract to reach the thalamus. Second order neurons synapse in thalamic nuclei with third order neurons, which in turn send projections through the internal capsule and corona radiate to the postcentral gyrus of the cerebral cortex.

- First-order neurons; the majority of first-order neurons send the proximal end of their axons into the SC via dorsal (sensory) spinal root at each level. Once in the dorsal horn, in addition to synapsing with second-order neurons, the axons of first-order neurons may synapse with interneurons, sympathetic neurons and ventral horn motor neurons.
- **Second-order neurons;** pain fibers may ascend or descend one to three SC segments in Lissauire's tract before synapsing with second-order neurons in the gray matter of the ipsilateral dorsal horn. In many instances they communicate with second-order neurons through interneurons.

SC gray matter was divided by Rexed into 10 laminae. The first 6 laminae, which make up the dorsal horn, receive all afferent neuronal activity, and represent the principal site of modulation of pain by ascending and descending neural pathways. Second-order neurons are either nociceptive-specific or wide dynamic range (WDR) neurons.

Nociceptive-specific neurons serve only noxious stimuli, but WDR neurons also receive non-noxious afferent input for Aβ, Aδ, and C fibers. **Nociceptive specific neurons** are arranged somatotopically in lamina 1 and have discrete, somatic receptive fields and respond only to high threshold noxious stimulation. **WDR neurons** are the most prevalent cell type in the dorsal horn. Although they are found throughout the dorsal horn, WDR neurons are most abundant in lamina 5. During repeated stimulation, WDR neurons characteristically increase their firing rate exponentially in a graded fashion ("wind-up") even with the same stimulus intensity.

Most nociceptive C fibers send collateral to, or terminate on, second-order neurons in lamina 1, 2, and to a lesser extent lamina 5. In contrast, nociceptive Aδ fibers synapse mainly in lamina 1, 5 and to a lesser degree lamina 10. **Lamina 1** responds primarily to noxious (nociceptive) stimulation from cutaneous and deep somatic tissues.

**Lamina 2**, also called the **substantia gelatinosa**, contains many interneurons and is believed to play a major role in processing and modulating nociceptive input from cutaneous nociceptors. It is also of special interest because it is believed to be a major site of action for opioids. **Lamina 8 and 9** make up the anterior (motor) horn. **Lamina 7** is called the intermediolateral column and contains the cell bodies of preganglionic sympathetic neurons.
Visceral afferent terminate primarily in lamina 5, and to a lesser extent lamina 1. **Lamina 5** responds to both noxious and non-noxious sensory input and receives both visceral and somatic pain afferent.

The axons of most second-order neurons cross the mid-line close their level of origin (at the anterior commissure) to the contralateral of the SC before they form the spinothalamic tract and send their fibers to the thalamus, the reticular formation, the nucleus raphe magnus, and the periaqueductal gyrus. Other ascending pain pathways are also important e.g. spinoreticular, spinomesencephalic, spinohypothalamic, and spinotelencephalic tracts.

Somatic and visceral afferents are fully integrated with skeletal motor and sympathetic symptoms in the SC, brain stem, and higher centers.

### 2.3 PHYSIOLOGY OF PAIN (NOCICEPTION):

#### 2.3.1 Central modulation of pain:

Modulation of pain occurs peripherally at the nociceptors, in the SC, or in the supraspinal structure. **The central modulation** can either inhibit (suppress) or facilitate (aggravate) pain.

- **Facilitation**: neurochemical mediators of central sensitization include substance P (sP), VIP, calcitonin gene-related peptide (CGRP), cholecystokinin (CCK), angiotensin, and galanin as well as the excitatory amino acids (AAs) L-glutamate and L-asparate (sP and CGRP are the most important of these peptides, while glutamate is the most important excitatory AA). These substances trigger changes in membrane excitability by interacting with G protein-coupled membrane receptors on neurons activating intracellular second messengers. A common pathway is an increase in intracellular calcium. The AAs are believed to be largely responsible for the induction and maintenance of central sensitization.\(^{(66)}\)

- **Inhibition**: transmission of nociceptive input in the SC can be inhibited by segmental activity in the cord it-self, as well as descending neural activity from supraspinal centers.
The inhibitory neurotransmitters (somatostatin, ACh, enkephalin, β-endorphin, norepinephrine, GABA, and glycine) produce a hyperpolarization of the postsynaptic membrane called the inhibitory postsynaptic potential. They modulate nociceptive activity in the dorsal horn. **Glycine** and **GABA** are the **most common inhibitory neurotransmitters** within the CNS. They likely play an important role in segmental inhibition of pain in the SC. (67)

- **Supraspinal inhibition:** several Supraspinal structures and fibers (descending pathways) down the SC to inhibit pain in the dorsal horn. Axons from these tracts act presynaptically on primary afferent neurons and postsynaptically on second-order neurons (or interneurons). These pathways mediate their antinociceptive action via α₂-adrenergic, sertonergic and opiate (μ, δ, and κ) receptor mechanism (the antidepressants-monoamines, block reuptake of catecholamine and serotonin). The endogenous opiate system act presynaptically to hyperpolarize primary afferent neurons and inhibit the release of sP. In contrast, exogenous opioids may preferentially act postsynaptically on the second-order neurons or interneurons in the substantia gelatinosa.

2.3.2 **Muscarinic receptors:** Excitatory and inhibitory receptors exist on the postsynaptic cell. Both opioid and α₂-adrenergic receptors have been described on or near the terminals of unmyelinated peripheral nerves.

Five Muscarinic receptors subtypes have been cloned. (68) Receptor binding studies with non-selective compounds have shown that most muscarinic binding sites are localized in the **substantia gelatinosa** in the dorsal horn, and in the motor neuron areas. The area is presumably the one involved in antinociceptive effects. The relatively selective M1 and M2 blocking agents (pirenzepine and FDX 116) both inhibit carbachol-induced antinociceptive effect, suggesting that both types of receptors play a role. An interaction between adrenergic and cholinergic appears likely. Autoradiographic studies reveal the existence of muscarinic receptors; both M1 and M2 in **lamina 2 and 3** of the SC. Immunohistochemical studies in the
rat model have consistently revealed the presence of cell bodies staining for choline acetyltransferase in lamina 3, 4 and 5, which are dendritic.

2.3.3 Clinical application of muscarinic stimulation:

Exogenous administered ACh has a very short duration of action because it is inactivated rapidly by acetylcholinesterase (at the synapse). Nonetheless, the most efficient method for prolonged stimulation of the spinal muscarinic system is by the administration of long-acting anticholinesterase, which has shown high antinociceptive efficacy and lack of neurotoxicity.

Spinal administration of acetylcholinesterase inhibitors, such as neostigmine, inhibits breakdown of an endogenous spinal ACh neurotransmitter. (69)

Release of ACh in the SC is stimulated by pain, systemic opioids, and spinal $\alpha_2$-agonists. Further analgesic effects of ACh may involve stimulation of production of nitric oxide, as increased level of SC nitrite are observed after spinal administration of ACh. Although the nicotinic mechanisms in antinociception are more controversial, both types of cholinergic receptors have been identified in the nociceptive pathways. As nicely discussed by Ping-Heng Tan et al, in this issues, substantia gelatinosa of the human SC is especial rich in muscarinic.

In the spinal cord, concentrations of acetylcholine and noradrenalin, and synthesis of nitric oxide (NO) are increased after administration of cholinomimetic substances. The former mechanism has been proposed to be involved in cholinergic analgesia in acute nociception, such as in postoperative pain, while the NO-mediated mechanism would be more important in chronic pain after nerve injury. Although it has recently been shown that central muscarinic antinociception is highly dependent on the M1 receptor subtype, analgesia may be induced via stimulation of both postsynaptic M1 and presynaptic M2 muscarinic receptors in the brain. (70)

Another mechanism of analgesia is the muscarinic presynaptic inhibition of glutamate secretion. Finally, antinociception and analgesia have been
demonstrated by activation of muscarinic receptors in peripheral nerve endings. (71)

In preliminary dose-response studies of neostigmine (6.25, 12.5, and 50 µg) as an additive to low-dose (7.5mg) bupivacaine anaesthesia conducted in volunteers and surgical patients, intrathecal (IT) neostigmine provided analgesia in doses ≥ 10µg (surgical patients "as release of Ach is enhanced by pain") to ≥ 50 µg (volunteers). (72)
3. SPINAL NEOSTIGMINE

Neostigmine consists of a carbamate moiety and a quaternary ammonium group. The former provides covalent bonding to acetylcholinesterase. The later renders the molecule lipid-insoluble, so that it cannot pass through the BBB. (73)

3.1 MECHANISM OF ACTION:

Neostigmine is an indirect cholinomimetic agent. It produces its primary effects by inhibiting the action of acetylcholinesterase, which hydrolyzes ACh to choline and acetic acid. By inhibiting acetylcholinesterase, the indirect-acting drug increases the concentration of spinal endogenous ACh.

This drug is, in effect, amplifiers of endogenous ACh and act primarily where ACh is physiologically release. It combines reversibly with Acetylcholinesterase by the formation of an ester linkage, witch lasts about 30 minutes. (74)

3.2 PHARMACOKINETIC:

The pharmacokinetic of neostigmine administered by bolus injection is linear with respect to bolus injection. The time of the peak concentration ranged from 5-30 min (this the range in time to peak concentration reported for pethidine). (75) The absorption phase was followed by a biexponential distribution and elimination phase. Diffusion in CSF plays a major role in drug distribution.

There is a sustained plateau of increased ACh concentration in CSF after IT neostigmine and lack of correlation between CSF ACh concentration and analgesia. It is likely that CSF neostigmine concentration even after the lowest dose of neostigmine is an adequate to significantly inhibit cholinesterase in CSF.
3.3 **DOSAGE OF INTRATHECAL NEOSTIGMINE:**

The effectiveness - reduced pain scores and low consumption of rescue analgesics - of subarachnoidally administered neostigmine in doses of 10-100 µg has been demonstrated in controlled clinical studies.\(^{76}\)

3.4 **SIDE EFFECTS OF IT NEOSTIGMINE:**

Intrathecally administered neostigmine could produce side effects by **local spinal actions** (lower extremity weakness, and hypertension) or by **central distribution** (nausea, vomiting and sedation).

The incidence and severity of these adverse effects from IT neostigmine appears to be affected by dose, method of administration, and the baricity of solution.

Addition of 50µg neostigmine significantly improve sensory and motor block but also lead to delay in achievement of discharge criteria for ambulatory anaesthesia and to a high incidence of nausea and vomiting (>50%). Addition of even the smallest dose of neostigmine (6.25 µg) produced a high incidence of nausea and vomiting (30%) that was sever, repetitive, prolonged (2-6 h), and resistance to pharmacologic therapy.

Intrathecal neostigmine alone produces definitive analgesia in humans. In 28 normal healthy human volunteers, IT neostigmine (50-750µg) followed by catheter insertion and aspiration of CSF for analysis produce dose-dependent analgesia accompanied by dose-related motor weakness, decrease in deep tendon reflexes, urinary incontinence, genitourinary stimulation and nausea and vomiting. Nausea and vomiting were reduced by injecting it in a hyperbaric solution. This study provided the safety basis and defined the side effects to be monitored for subsequent clinical trials.

Currently available formulations contain the preservatives methyl– and propyl–paraben and are usually mixed with glucose to yield hyperbaric solutions. The safety of chronically administered IT neostigmine containing these additives was examined in animals.\(^{77}\) Chemically administered IT
neostigmine containing glucose and these additives failed to produce behavioral, chemical, or histopathological evidence of neurotoxicity.

In patients undergoing inguinal herniorrhaphy, IT neostigmine administered at 50 µg or 100 µg enhance the onset of tetracaine analgesia and provide analgesia for a period of about 6-9 hours. Adverse effects such as nausea, vomiting, and prolonged motor block were dose dependent.

In an attempt to evaluate IT neostigmine safety during cesarean section (S/C), neostigmine was administered with morphine intrathecally. Fetal heart rate (FHR) was monitored for 15 min prior to surgery and during surgery. IT neostigmine did not affect FHR in women prior to C/S and was well tolerated. It was associated with reduced postoperative morphine requirements, an affect that lasts approximately 10 hours. It produced dose-independent reduction in morphine use but a trend toward dose-dependent nausea.

Some studies have revealed that intrathecal neostigmine produced dose-dependent analgesia and adverse effects. \(^78\) \(^79\) However, other studies have shown that intrathecal neostigmine could produce a dose-independent analgesia and a dose-dependent incidence of adverse effects. \(^80\) Efforts, therefore, were made to reduce the undesirable adverse effects of IT neostigmine.

Hood et al, demonstrated that IT neostigmine enhanced side effects, such as nausea and vomiting, after i.v. opioid administration (alfentanil). \(^81\) Both IT neostigmine and i.v. alfentanil increased CSF ACh concentrations and produced analgesia. Neostigmine didn't enhance respiratory depression induced by i.v. alfentanil, although it does enhanced sedation and nausea.

A study was designed to compare the effects of the addition of IT neostigmine or IT morphine on the characteristics of SA with bupivacaine. \(^82\) IT 300 µg morphine produced long lasting analgesia with duration of about 10 hours compared to IT 50 µg neostigmine which resulted in postoperative analgesia lasting about 7 hours. The incidence of adverse effects was similar
for the two groups, except for pruritus, which occurred more frequently in the morphine group.

**Involuntary defecation** during the postoperative period was reported as an adverse effect with production of **poor analgesic** effects in patients suffering from ischemic pain or in patients undergoing cesarean section and orthopedic surgery under spinal anaesthesia. \(^{(83)}\)

Vomiting was not observed following intra-operative spinal administration of neostigmine in patients under enflurane anaesthesia. \(^{(84)}\) The incidence of vomiting and hypotension was reduced in volunteers treated intrathecally with a hyperbaric solution of neostigmine.

The effect of a prophylactic single dose of i.v. dexamethasone (10mg) injection on the incidence and severity of postoperative nausea and vomiting after IT injection of tetracaine plus neostigmine 100 µg was evaluated. \(^{(85)}\) It was found that, it didn't reduce the incidence of emesis in patients receiving SA during inguinal herniorrhaphy.
4. LOCAL ANAESTHETICS

Regional anaesthetic techniques depend on a group of drugs that produce transient reversible loss of sensory, motor, and autonomic function in a discrete portion of the body.

4.1 CLASSIFICATION AND STRUCTURE-ACTIVITY RELATIONSHIPS:

Local anaesthetics consist of a lipophilic group – usually a benzene ring (aromatic ring) - separated from a hydrophilic group -usually a tertiary amine- by an intermediate chain that includes ester or amide linkage. Local anaesthetics are weak bases that are usually carrying a positive charge at the tertiary amine group at physiological pH.

The nature of the intermediate chain is the basis of the classification of Local anaesthetics as esters or amides. Physiochemical properties of Local anaesthetics depend on:

- The substitutions in the aromatic ring,
- The type of linkage in the intermediate chain, and
- The alkyl groups attached to the amine nitrogen.

Potency correlates with lipid solubility, and depends on the ability of the Local anaesthetic to penetrate a hydrophobic environment.

Onset of action depends on many factors, including, the relative concentration of non-ionized lipid-soluble form and the ionized water soluble form.

Duration of action is associated with plasma protein binding (α1-acid glycoprotein).
4.2 MECHANISM OF ACTION:

They block the initiation and propagation of action potential by blocking the voltage-dependent sodium channels. They bind to specific receptors on the inner surface of sodium channel.\(^{(86)}\)

Local anaesthetics are weak bases and at physiological pH, both charged forms exist (depending upon the pKa of Local anaesthetics which is usually 8-9). The free un-dissociated base (lipophilic) penetrates the nerve sheath and axonal membrane to reach its site of action. The cationic (charged; hydrophilic) form is probably responsible for the sodium-channel blockade.

Quaternary local anaesthetics block the channel from inside (hydrophilic pathway). They reach their site of action via an open channel. Tertiary or secondary amine Local anaesthetics penetrate the sheath and axonal membrane in the uncharged form (lipophilic pathway) to block the channel. However, they can also act from the inner surface of the membrane if they are in the cationic form.

Small diameter unmyelinated fibers are most susceptible then large myelinated ones. Pain sensation is abolished first, followed by cold, warmth, touch and pressure.

Local anaesthetics solution injected into the CSF spreads away from the site of injection and the concentration of the solution decreases as mixing occurs. A differential blockade of fibers occurs because small fibers are blocked by weaker concentrations of Local anaesthetic solution.

4.3 LOCAL ANAESTHETICS USED IN SPINAL ANAESTHESIA:

The choice of Local anaesthetic for a specific procedure is usually based on the duration of action (surgery) required. Procaine is short acting; lidocaine has an intermediate duration of action; tetracaine, bupivacaine, and ropivacaine are long-acting drugs.
4.3.1 Procaine:

Procaine is the oldest member of the ester Local anaesthetic family (1904) and still remains in clinical use.

The synthesis of procaine for peripheral nerve block was coincident with the first attempts at achieving anaesthesia in the subarachnoid space, and procaine was one of the first Local anaesthetics used for SA.

It is a water-soluble agent with poor lipid solubility. Toxicity with procaine is very uncommon, unless massive doses are administered or large doses are injected directly into the blood stream.

SA can be performed with 50-200 mg of the 10% solution of procaine mixed with equal volumes of 10% glucose, or as the lyophilized crystal diluted in glucose or CSF. The duration of subarachnoid block would be 30-60 min. Procaine has been mixed with tetracaine or lidocaine for SA for c/s to accentuate the density of the block in the past to achieve an improved quality of SA.

4.3.2 Lidocaine:

The discovery in 1948 by Lofgren in Sweden of lidocaine began the aminoamide era. Lidocaine proved to be excellent introduction for the amide agents because of its versatility, clinical efficacy, and reasonable clinical toxicity range. In the subarachnoid space, rapid complete anaesthesia is achieved with an intermediate duration.

Lidocaine is the most commonly selected agent for short-duration SA. Lidocaine is used for SA in the 2-5% range, either as isobaric or hyperbaric solutions. The most common preparation of lidocaine for SA is a pre-mixed hyperbaric solution of 5% in 7.5% glucose. When 50 - 75 mg are injected into the average-sized adult, rapid onset of dense and complete motor block occurs, which lasts for 60-90 min. this can be prolonged 20-30% by the addition of epinephrine. When concentration is reduced to 1.5% lidocaine with the same concentration of dextrose, the clinical outcome is indistinguishable. For isobaric lidocaine SA, 2-3ml of the 2% solution are
injected, which result in a slightly slower onset of comparable anaesthesia with a slightly longer duration.\(^{(88)}\) This can be explained by the delayed peak level in the plasma and delayed elimination half-life from the subarachnoid space compared to the hyperbaric solution. Lidocaine can be diluted with sterile water for a hypobaric application.

Active controversy exists about whether lidocaine is neurotoxic in the subarachnoid space or whether the concentration (5\%) may be the etiology. Cases of cauda equina syndrome have been associated with 5\% lidocaine with continuous SA and less frequently, with single-shot SA.\(^{(89)}(90)\)

4.3.3 **Tetracaine:**

Tetracaine is an ester local anaesthetic belonging to the procaine group. It is a chemical derivative of procaine with **higher lipid solubility** (100 times than procaine), potency, and duration of anaesthesia. Release of tetracaine led to its rapid acceptance as the most popular agent for SA; which it remains. It is the **agent most commonly** used for SA in the US.

The 1\% solution is included in most commercial available trys for SA. The 1\% solution is mixed with equal volumes of 10\% dextrose for hyperbaric, with preservative-free sterile water for hypobaric and with the patient's CSF for an isobaric SA.

When 0.5\% tetracaine is used for isobaric SA, complete motor block and duration of anaesthesia of 180 minutes or longer is achieved. In contrast to bupivacaine SA, a dense, long-acting motor block is achieved with tetracaine.

4.3.4 **Bupivacaine:**

Bupivacaine was created by modification of an existing local anaesthetic (mepivacaine) with intent to create a **more potent, longer** local anaesthetic.\(^{(91)}\) The duration of action of bupivacaine exceeds lidocaine by a two to three times or more. Limited placental transfusion combined with the selective increased potency for sensory block and relatively decreased
potential for motor block at lower concentration, established efficacy for obstetric anaesthesia.

At very low concentrations (< 0.25%), sensory anaesthesia and analgesia separate and achieving analgesia without complete motor block is possible and is used extensively for acute postoperative pain control.

Bupivacaine is commonly selected for SA. The atypical dose is 15mg of bupivacaine, prepared as 3 ml of 0.5% plain bupivacaine. Epinephrine accentuates the intensity of the block, especially the motor block, but has no influence on the duration of the block. The duration of bupivacaine SA is comparable to tetracaine (150-180 mints), and it is longer in geriatric patients. Dilution and reduction of the total dose of hyperbaric bupivacaine reduced the duration of the block by 50% and reduced the total time to release from an ambulatory unit by >50%. (92)

4.3.5 Ropivacaine:

Ropivacaine is the newest addition to the clinical options of regional anaesthesia. It is similar chemically to bupivacaine. Preliminary work suggests that ropivacaine has lower potency and shorter motor block in the subarachnoid space than bupivacaine with a greater degree of differential block in dilute solutions. (93) At equivalent concentrations ropivacaine appears to be less likely than bupivacaine to cause cardiac arrhythmias and collapse; resuscitation is more likely than successful if toxicity does occur.
OBJECTIVES

The present study is designed to:

♦ Evaluate the effects of the addition of different doses of neostigmine on the characteristics of spinal anaesthesia using bupivacaine and to,

♦ Assess their postoperative analgesic efficacy and safety in patients undergoing infra-umbilical surgery under spinal anaesthesia.
Chapter 2

PATIENTS AND METHODS
PATIENTS AND METHODS

1. HOSPITALS AND PERIOD OF STUDY:

This study was performed at KHARTOUM teaching hospital (KTH) and SOBA university hospital (SUH). The well equipped theatres and the facilities of observation and follow up the patients were the main reasons for selecting these hospitals. The study extended from 1st of March 2003 to 15th February 2004.

2. STUDY DESIGN:

The study protocol was approved by the medical committee of our university department and hospitals. Written informed consents were taken from all patients. Sixty Sudanese ASA 1-2 patients, scheduled for elective infra-umbilical surgery under spinal anaesthesia were included in this study.

This is a prospective comparative study in which the effects of different doses of neostigmine on the characteristics of SA were studied and compared. Patients were allocated randomly into one of three groups, each group was 20 patients:

- Group 1 received hyperbaric IT bupivacaine (0.5%) 15 mg + 0.5 ml dextrose (5%).
- Group 2 received hyperbaric IT bupivacaine (0.5%) 15 mg + IT neostigmine (50µg) diluted in 0.5 ml dextrose (5%).
- Group 3 received hyperbaric IT bupivacaine (0.5%) 15 mg + IT neostigmine (100µg) diluted in 0.5 ml dextrose (5%).

3. INCLUSION CRITERIA:

- Patients of fitness rating of ASA grade 1 and 2.
- Co-operative patients.
- Patients undergoing elective surgical procedure under SA and who were planned to maintain a supine position throughout the surgery.

4. **EXCLUSION CRITERIA:**

- Patients at age < 20 years and > 70 years.
- Patients of ASA grade > 2.
- Deaf and dumb patients or both.
- Patients with allergies to any of the test drugs.
- Patients in whom there was absolute or relative contraindication to SA.
- Prolonged surgery in which the patients received any of general anaesthesia support.
- Presence of preoperative nausea or vomiting.
- Pregnant patients or planned for cesarean section.
- Patients who have received any pre-medications.

5. **PATIENT INTERVIEWS:**

   General characteristics of patients, obtained from history and examination, were recorded in a special designed form. Personal data; name, age, and sex, baseline vital signs (pulse, BP, and respiratory rate), ASA grade, time of onset of anaesthesia and kind, onset, and duration of operation were recorded.

   All patients were inquired about their past medical, surgical, and anaesthetic history and whether the patient has experienced any complications following a previous anaesthetic exposure. Agents taken or allergy to any were asked about and checked.

   A full physical examination was conducted to all subjects with emphasis on the cardiovascular, respiratory, CNS, lumbar site and airway assessment. Routine preoperative investigations were observed.
6. **PREPARATION BEFORE CONDUCTION OF SPINAL ANAESTHESIA:**

    In the holding room, an explanation of the procedure and its benefits was given. An i.v. line was inserted into the forearm using 18-gauge i.v. cannula, and all patients were given 500 ml of normal saline (0.9) solution as a circulatory preload.

    Materials necessary for aseptic performance of drug dilution and SA were prepared.

    Resuscitation equipments and drugs were prepared and kept within reach. Insulin 1ml syringe was used to make precise dosing.

7. **CONDUCTION OF SPINAL ANAESTHESIA:**

    Spinal anaesthesia was performed in the operating room at the L3-L4 interspace with the patient in the sitting position.

    - The back was exposed, scrubbed using savlon and sterilized with spirit.
    - Infiltration of skin and subcutaneous tissue over the interspace chosen were done by 3 ml of 2% lidocaine.
    - A 0.5 mg neostigmine methyl sulphate was withdrawn into a sterile 5 ml syringe, then diluted to a total of 5 ml of dextrose (5%) in group 2 (0.5 ml = 50µg neostigmine), or to 2.5 ml in group 3 (0.5 ml = 100µg neostigmine).
    - A 0.5 ml of the diluted neostigmine was withdrawn into an insulin syringe and added to the 3 ml hyperbaric bupivacaine (15 mg).
    - A sterile disposable 22-gauge spinal needle was then slowly introduced until dura was puncture and free backflow of CSF checked.
    - The premixed drug was then injected slowly; over duration of approximately 30 seconds.
- The puncture site was covered by sterile gauze that was held in place by means of adhesive Elastoplasts.
- The patients were positioned horizontally in the supine position and they were kept at the same position throughout surgery.

8. **MONITORING AND ASSESSMENT OF PAIN AND OTHER OBSERVATIONS:**

   Non-invasive measurement of BP, PR, RR and oxygen saturation (Spo2) were monitored, every 3 minutes for the initial 15 minutes, then every 5 minutes throughout the surgery, and then, except, Spo2, every 30 minutes in the postanaesthesia care unit (PACU) for 2 hours. **Bradycardia** (PR < 60 beat/minutes) was treated with i.v. atropine (0.5 mg). IVF boluses and incremental doses of ephedrine (5mg) were given to those patients whose **systolic BP fell below 100 mmHg**.

   Observation of retching was used to evaluate adverse effects (e.g. nausea, vomiting, and sedation). **Nausea** was scored by the patient using the 10-cm visual analogue score (VAS) (0-10). Nausea that scored greater than 2 of the VAS at any time, or **vomiting**, more than once, was treated initially with i.v. 10 mg Metoclopramide followed by Ondansetron 4 mg IV, if necessary. The number of patients having nausea (at any degree) or vomiting (at any point) intra-operatively was noted and recorded.

   The level of sensory block was tested by pinprick, and the sensory level at 5 and 10 minutes intervals, after drug injection, were recorded.

   The severity of postoperative pain was measured using a 10-cm VAS (0 = no pain, 10 = the worst possible pain). The 24 hour VAS score reflected the patient's assessment of total pain experience for the previous 24 hour post-intrathecal drug administration.

   The duration of absolute analgesia was measured from the time of drug administration to the time when the VAS-pain score was greater than zero.
The time of administering the first dose of diclofenac for postoperative pain, and the number of diclofenac administered were, also recorded. The postoperative analgesia was provided with IM diclofenac 75 mg if the VAS score was $\geq 4$ and can be repeated 8 hourly as necessary.

The duration of motor block was assessed using the Bromage scale and was recorded from the time of drug administration to the time when patients able to lift their legs in bed, against gravity (grade 2).

Respiratory depression was defined by a RR $< 10$ breaths/minutes. Scores of postoperative pain, any side effect, and patient evaluation were recorded at 4 hours interval for 24 hours post-IT drug administration.

9. METHODS OF DATA COLLECTION:

The following techniques and tools were used;

- Scheduled observation form.

- The severity of postoperative pain is measured using a 10 cm VAS, during rest 4 hourly or whenever patient requested analgesia.

- Assessment of the level of sedation was made intra-and postoperatively using an objective score based on eye opening (eyes open spontaneously = 0, in response to speech = 1, and in response to physical stimulation = 2).

- the Bromage scale was used to evaluate the duration of motor blockade: “no block” (the ability to flex the knees and feet), “partial block” (ability to flex the knees and resist gravity with full, movement of the feet), “almost complete block” (inability to flex the knees but retained ability to flex feet), and “complete block” (inability to move the legs or feet).

- Nausea was scored by the patient using the 10-cm VAS-N score, which consists of a 10-cm line, with 0 equaling 'no nausea' and 10 equaling 'worst possible nausea'.
10. DATA ANALYSIS:

The data collected were analyzed and compared by analysis of variance with paired-samples T test using a manual master sheet and SPSS software program. Data were expressed as means ± standard deviation of the mean or median and the (25th-75th) percentile confidence interval as appropriate. A value of p<0.05 was regarded as a statistically significant differences.
Chapter 3
RESULTS, TABLES, AND FIGURES
RESULTS

Sixty patients were included in this study, twenty in each group. The three groups showed no differences regarding ASA physical status, age, sex, preoperative vital signs, and surgical time (p >0.05) (Table 1) (Fig. 1, 2, 3).

The onset of anaesthesia, as measured by the level to pinprick at 5 and 10 minutes, was significantly earlier for group II and III patients. Median values (25%–75% percentile confidence) of thoracic (T) dermatome to a pinprick on the skin were being T8 (7–9) for group II and T8 (7–8) for group III compared with the median value for group I patients T10 (9–10.7) at 5 minutes (P <0.05). At 10 minutes, it was T6 (4–6) for group II patients and T5 (5–5) for group III patients compared with the median for group1 patients T7 (5–8) (p < 0.05). However the difference between group II and III was not significant at 5 minutes (p=0.287) (Table 2) (Fig. 4). The three groups showed no differences regarding intraoperative data. (Fig. 5)

The duration of absolute analgesia, which was measured between the time of drug administration to the time when the VAS pain score was greater than zero, group III patients showed a much longer duration of complete analgesia with an average of 6 ±1.4 hours, compared to 3.5 ± 1 hours for group I patients (p < 0.001) and 4.7 ±1.4 hours for group II patients (p = 0.017) (Table 3) (Fig. 6, 7).

The mean time until the first dose of IM diclofenac administration was longer for group III patients (7.7 ± 2.1 hours) compared with group I patients (4.9 ± 1.3 hrs) ( p < 0.001) and group II patients (6.3 ± 1.8 hrs) ( p=0.045) (Table 4) (Fig. 8).

Again comparing group I and group III patients, there was a significant difference in the number of IM Diclofenac injections requested in the 24 hr post surgery (Fig. 9). The median number of injections for group I, group II,
and group III patients was, respectively, 2.5(1.25–3), 1(1–1), and 1(1–3) and P was less than 0.05 between all groups. All patients of group I (100%) needed postoperative analgesia and the time of rescue analgesia administration ranged from (2.1–7.6 hours) postoperatively. In group II patients, 13 (65%) needed postoperative analgesia. The time of rescue analgesic administration ranged from (3–11.4 hrs). In group III patients, 18 (90%) needed postoperative analgesia and the time of rescue analgesic administration ranged from (4.5–12.6 hrs) postoperatively.

Intraoperative hypotension (systolic BP < 100 mmHg or a decrease in systolic BP >20% below preanesthetic baseline) was recorded in 9 patients in group I (45 %), in 8 patients in group II (40%), and in 3 patients in group III (20%). This difference in incidence between the three groups was not significant (p > 0.05) (Fig. 10). There was no significant differences in the total i.v. ephedrine injections requested intraoperatively (p > 0.05) (Table 5).

Three patients in group I (15%) had Intraoperative bradycardia 71.6 minuets (40 – 95) after the spinal injection (Table 6). Four patients in group II (20%) had Intraoperative bradycardia 57.5 minutes (15 – 95 min) after the spinal injection. Two patients in group III (10%) had Intraoperative bradycardia 90 minuets (30 – 150) after the spinal injection. This difference in incidence between the three groups was not significant (p > 0.05). All were being treated with i.v. atropine 0.5 mg increments. There was significant differences in the total i.v. atropine injections requested intraoperatively (p < 0.05) (Fig. 11).

The Intraoperative VAS–Nausea and time to first episode of nausea or occurrence of vomiting were different among the groups (Table 7). Nausea was recorded in 5 patients in group I (25%), in 7 patients in group II (35%), and in 4 patients in group III (20%) (Fig. 12).
There was significant difference in the time to first episode of nausea between group II and group III compared with group I (p < 0.001) and between group II and group III (p=0.026) (Fig. 13).

Patients in group II and group III demonstrated a highly significant increase in the severity of nausea compared with group I, means of VAS–Nausea score were 10.5 ±2.1 and 10.5 ±2.1 for group II and group III, respectively, compared with 2.4 ±0.2.5 for group I (p < 0.001). However, the difference between group II and group III was not significant (p = 0.239). (Fig. 14)

Patients in group II and group III demonstrated a significant increase in the incidence of vomiting compared with group I (p < 0.05). However, patients in group II showed a significantly higher incidence in severity of vomiting than those in group III (p < 0.05) (Table 8).

None of patients in group I required any treatment for nausea and vomiting. In group II patients, 5(25%) of them needed i.v. metoclopramide (10mg) injection and then, 3(15%) of them required supplement with i.v. Ondansetron (4mg). In group III patients, 4(20%) needed i.v. metoclopramide (10mg) injection and then, 3(15%) of them required supplement with i.v. Ondansetron (4mg) (Fig. 15).

Motor block was significantly prolonged for group III patients (5.8±1.6 hr) compared with group I participants (4.3±1.5 h) (p =0.002). However, the differences between group I patients and group II patients (4.8±1.9 h) and between group II and group III patients were not significant (p = 0.150 and 0.16, respectively) (Table 9).

One patient from each group, group II and III, had a bowel movement 150 minutes and 120 minutes, respectively, after the spinal injection (Table 10).

None of the patients had any episodes of motor weakness. Sedation scores were comparable in all the groups. No patient had a sedation score of
more than 0 at any time. No delayed adverse effects were observed during the postoperative follow up.
### Table (1):

**Demographic data of the patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.5 ±16.3</td>
<td>48.9 ±16.3</td>
<td>44.9 ±15.3</td>
</tr>
<tr>
<td>ASA (1:2)</td>
<td>18/2</td>
<td>20/0</td>
<td>20/0</td>
</tr>
<tr>
<td>Sex (M: F)</td>
<td>15/5</td>
<td>11/9</td>
<td>13/7</td>
</tr>
<tr>
<td>Surgical time (min)</td>
<td>88.2 ±37.1</td>
<td>94.7 ±36.1</td>
<td>84.3 ±35.7</td>
</tr>
<tr>
<td>Respiratory rate (min)</td>
<td>19.9 ±3.2</td>
<td>18.8</td>
<td>18.6 ±1.6</td>
</tr>
<tr>
<td>Pulse rate (min)</td>
<td>91.4 ±18.8</td>
<td>94.7 ±15.6</td>
<td>100.3 ±20.5</td>
</tr>
<tr>
<td>BP (mmHg)</td>
<td>92.8 ±10.8</td>
<td>91.6 ±12.4</td>
<td>96.5 ±14.8</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>97.9 ±1.3</td>
<td>97 ±18.1</td>
<td>98.1 ±1.2</td>
</tr>
</tbody>
</table>

Note: Data are expressed as mean ± SD. No statistically significant differences were observed (p > 0.05)

### Table (2):

**Level to pinprick at 5 and 10 minutes**

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Pinprick (5 min)*</td>
<td>10(9 - 10.7)</td>
<td>8(7 - 9)</td>
<td>8(7 - 8)</td>
</tr>
<tr>
<td>Pinprick (10 min)*</td>
<td>7(5 - 8)</td>
<td>6(4 - 6)</td>
<td>5(5 - 5)</td>
</tr>
</tbody>
</table>

Pinprick: the thoracic dermatome anaesthesia to a pinprick on the skin. *Median (25% - 75% percentile confidence).
**Table (3):**

**Postoperative analgesia**

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Duration of absolute analgesia (hrs)^</td>
<td>3.5 ±1*</td>
<td>4.7 ±1.4*</td>
<td>6 ±1.4*</td>
</tr>
<tr>
<td>Overall 24-hour VAS pain+</td>
<td>19.6 ±6.4*</td>
<td>12.5 ±3.1*</td>
<td>10.2 ±2.6*</td>
</tr>
</tbody>
</table>

* Note: Data are expressed as means ± SD.
^ P = 0.003, group 1 versus group 2, p < 0.001, group 1 versus group 3, p = 0.017, group 2 versus group 3.
+ P < 0.005

**Table (4):**

**Need for postoperative analgesia**

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Time to first rescue analgesia (hrs)^</td>
<td>4.9 ±1.3*</td>
<td>6.3 ±1.8</td>
<td>7.7 ±2.1</td>
</tr>
<tr>
<td>No. of patients Received diclofenac injection</td>
<td>20(100%)</td>
<td>13(65%)</td>
<td>18(90%)</td>
</tr>
<tr>
<td>Number of IM diclofenac dose injection for each patient in 24 hª</td>
<td>2.5 (1.25 – 3)</td>
<td>1(1 – 1)</td>
<td>1(1 – 2)</td>
</tr>
</tbody>
</table>

* Note: Data are expressed as means ± SD. Other data are expressed as Median (25% - 75% percentile confidence).
^ P = 0.01, group 1 versus group 2, p < 0.001, group 1 versus group 3, p = 0.045, group 2 versus group 3.
ª P < 0.001, group 1 versus group 2, p = 0.001, group 1 versus group 3, p = 0.004, group 2 versus group 3.
### Table (5):

**Intraoperative hypotension**

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>No. of patients developed intraoperative hypotension (%)</td>
<td>9(45%)</td>
<td>8(40%)</td>
<td>4(20%)</td>
</tr>
<tr>
<td>Onset to first hypotension (min)*</td>
<td>34.7 ±29.7</td>
<td>31 ±19.5</td>
<td>22.7 ±14</td>
</tr>
<tr>
<td>Total intraoperative ephedrine injection (mg)* ^</td>
<td>20 ±7</td>
<td>21.25 ±6.6</td>
<td>25 ±9.4</td>
</tr>
</tbody>
</table>

*Note: Data are expressed as means ± SD.
^p > 0.05

### Table (6):

**Intraoperative bradycardia**

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>No. of patients developed intraoperative bradycardia (%)</td>
<td>3(15%)</td>
<td>4(20%)</td>
<td>2(10%)</td>
</tr>
<tr>
<td>Onset to first bradycardia (min)*</td>
<td>71.6 ±28.4</td>
<td>57.5 ±38.6</td>
<td>90 ±84.8</td>
</tr>
<tr>
<td>Total intraoperative atropine injection* ^</td>
<td>1 ±0.16</td>
<td>0.75 ±0.1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Note: Data are expressed as means ± SD.
^P < 0.001
### Table (7): Intraoperative Nausea

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>No. of patients having nausea per total of patients</td>
<td>5/20 (25%)</td>
<td>7/20 (35%)</td>
<td>4/20 (20%)</td>
</tr>
<tr>
<td>Time to first nausea (min)^</td>
<td>213 ±60</td>
<td>115 ±63</td>
<td>63.7 ±37</td>
</tr>
<tr>
<td>Overall 24-hourVAS nausea^</td>
<td>2.4 ±0.24</td>
<td>10.5 ±2.1</td>
<td>10.5 ±2.1</td>
</tr>
<tr>
<td>No. of metoclopramide (10mg) injections</td>
<td>0</td>
<td>5/20(25%)</td>
<td>4/20(20%)</td>
</tr>
<tr>
<td>No. of ondansetron (4mg) injections</td>
<td>0</td>
<td>3/20(15%)</td>
<td>3/20(15%)</td>
</tr>
</tbody>
</table>

^Note: Data are expressed as means ± SD.

### Table (8): Intraoperative Vomiting

<table>
<thead>
<tr>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>No. of patients having vomiting per total of patients</td>
<td>1/20 (5%)</td>
<td>2/20 (10%)</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Median number of vomiting*</td>
<td>1(1 - 1)</td>
<td>10.5(9 - 12)</td>
<td>2(21 - 3)</td>
</tr>
</tbody>
</table>

*Median (25% - 75% percentile confidence).
Table (9):

<table>
<thead>
<tr>
<th>Motor block</th>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Motor block duration (hr)*</td>
<td>4.37 ±1.5</td>
<td>4.8 ±1.9</td>
<td>5.8 ±1.6</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Data are expressed as means ± SD. 

P = 0.150, group 1 versus group 2, p = 0.002, group 1 versus group 3, p = 0.164, group 2 versus group 3.

Table (10):

<table>
<thead>
<tr>
<th>Bowel movement</th>
<th>Group</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>No. of patients developed bowel movement (%)</td>
<td>0</td>
<td>1(5%)</td>
<td>1(5%)</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1: Demographic Data (Age)
Figure 2: Demographic Data (ASA)
Figure 4: Level to pinprick at 5 and 10 minutes
Figure 5: Intraoperative Data
Figure 6: Time of Postoperative Analgesia

![Bar chart showing the mean duration of absolute analgesia for different groups of patients. Group I has a mean duration of 3.5 hours, Group II has 4.7 hours, and Group III has 5.0 hours. The x-axis represents the group of patients, and the y-axis represents the mean duration of absolute analgesia in hours.]
Figure 7: 24-Hour VAS Pain Assessment
Figure 8: Time to First Rescue Analgesia

- Group I: 4.9 hours
- Group II: 5.3 hours
- Group III: 7.7 hours
Figure 9: Patients Requesting Postoperative Analgesia

- Group I: 100%
- Group II: 65%
- Group III: 90%
Figure 10: Intraoperative Hypotension and Bradycardia
Figure 11: Time to First Hypotension and Bradycardia

- Hypotension:
  - Group I: 34.7 min
  - Group II: 31 min
  - Group III: 22.7 min

- Bradycardia:
  - Group I: 71.6 min
  - Group II: 57.5 min
  - Group III: 90 min
Figure 12: Intraoperative Nausea and Vomiting
Figure 13: Time to First Nausea

- Group I: 213
- Group II: 115
- Group III: 63.7
Figure 14: 24-Hour VAS Nausea

- **Series 1**: 2.4
- **Series 2**: 10.5
- **Series 3**: 10.5

Mean Overall 24-Hour VAS Nausea

Group of patients
Figure 15: Number of Patients Received Metochlopromide and Ondansetron

<table>
<thead>
<tr>
<th>Antiemetic agents</th>
<th>Metochlopromide</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>Group II</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Group III</td>
<td>10%</td>
<td>15%</td>
</tr>
</tbody>
</table>
CHAPTER 4
DISCUSSION, CONCLUSIONS, RECOMMENDATIONS, REFERENCES AND APPENDIX
DISCUSSION

In phase I study assessment of intrathecal neostigmine in humans, Hood et al. found that broad range of intrathecal neostigmine from 150 – 500 µg could be safely used. When translated to per kg dosage in a 75-kg subject in their study, this corresponds to 2 – 7 µg/kg of intrathecal dose. In a study in patients undergoing orthopedic procedures involving use of epidural neostigmine, Lauretti et al. have taken into account the polar nature of neostigmine and thereby suggested that the extradural route can safely use 10 times the dose of intrathecal Neostigmine. Thus, the extradural dose equates to approximately 20 – 70 µg/kg. In a study in paediatric patients undergoing genitourinary surgery involving the use of caudal neostigmine, Batra et al. used caudal neostigmine in a dose range of 10 – 50 µg/kg. (94)

Considering the safe use of high doses of neostigmine by intrathecal, epidural and caudal routes, and based upon Hood's and other experiences, we chose to used intrathecal neostigmine at a dose of 50 µg and 100 µg for our clinical study.

Dose dependent analgesia with neuraxial administration of neostigmine was well known in animal and human tested. Hood et al. in an open label dose ranging study of intrathecal neostigmine revealed dose dependent-analgesia in humans with dose greater than 100 µg/kg.

Lauretti et al. in their study in patients undergoing vaginoplasty demonstrated that increasing doses of intrathecal neostigmine from 50 – 200 µg in combination with intrathecal morphine produced a dose-dependent pattern of analgesia, which allowed a reduction in the dose of each component. Tan and co-workers have also demonstrated dose-dependent analgesic effect of intrathecal neostigmine postinguinal herniorrhaphy. At the
same time, Nakayama et al. have demonstrated the dose-dependent analgesic effect of epidural neostigmine after abdominal hysterectomy.\(^{(95)}\)

However, other studies have shown dose-independent effect of neuraxial administration of neostigmine on postoperative pain relief and analgesic requirement. In pregnant patients, Krukaowski et al. have demonstrated that lower doses of intrathecal neostigmine (10, 30, and 100 µg) produced dose-independent analgesia lasting approximately 10 h in all the three groups. Similarly Lauretti et al. have shown dose-independent analgesia in patients undergoing vaginal hysterectomy in a dose range of 25 – 75 µg/kg Neostigmine. Same authors also demonstrated dose-independent analgesia with a combination of 20 mg intrathecal bupivacaine and 85 mg epidural lignocaine and intrathecal neostigmine (1, 2, or 4 µg/kg) in patients undergoing knee surgery.

Various studies with intrathecal or epidural neostigmine have also used neuraxial opioids.\(^{(96)(97)}\) Lauretti et al. demonstrated that, the combination of 25 µg of neostigmine with 25 µg fentanyl given intrathecally prolonged the time to first rescue medication (< 5 hours) and resulted in smaller number of IM Diclofenac injections in 24 hours.

In vitro and in vivo studies in animals have reported the release of spinal acetylcholine (ACh) in response to morphine. Opioids are known to stimulate norepinephrine and ACh release in the dorsal horn of spinal cord and thereby potentiate the effect of neostigmine.\(^{(98)}\) Dose-dependent increase in CSF norepinephrine and ACh has been demonstrated in sheep and man after intravenous opioids. This spinally released norepinephrine is believed to act on \(\alpha_2\)-adrenoceptors on spinal cholinergic neurons to cause ACh release.

Our study did not involve use of any systemic or neuraxial opioids and therefore simply represents a dose response curve to the increasing doses of spinal neostigmine. Our result was consistent with Hood's et al and Tan et al. A significant prolongation of postoperative complete analgesia and the time
for the first dose of diclofenac was seen with increasing doses of neostigmine from 50 – 100 µg compared with control group. The duration of complete analgesia increased from 4.7 ±1.4 h with 50 µg neostigmine to 6 ±1.4 h with a dosage of 100 µg compared to 3.5 ±1 h with bupivacaine alone. Not only did the postoperative analgesia increased but also the total analgesic requirement and number of rescue doses of analgesic decreased with increasing doses of spinal neostigmine.

The intrathecal administration of cholinergic receptor agonists or cholinesterase inhibitors produces an antinociceptive effect, which is mediated by spinal muscarinic receptors in animals, this analgesia have also been confirmed in human studies. (99)

Studies demonstrated the existence of muscarinic receptors, both M₁ and M₂, in laminae 2 and 3 of the spinal cord. Immunohistochemical studies in the rat model have consistently revealed the presence of cell bodies staining for choline acetyltransferase in laminae 3, 4 and 5, which are dentritic, arborized to laminae 1, 2, and 3 that predominantly process afferent nociceptive impulses. These results indicate that the muscarinic cholinergic system of the lumbar spinal cord is intrinsic. Intrinsic spinal cholinergic terminals are presynaptic to primary afferents. Taken together, these studies provide strong evidence for processing of afferent impulses of the intrinsic spinal cord cholinergic system. It has been suggested that acetylcholinesterase inhibitors act on the ACh released from those intrinsic spinal terminals.

Neostigmine, an anticholinesterase inhibitor, may cause an accumulation of ACh at the muscarinic receptors in the dorsal horn when administered intrathecally. Thus, increased spinal levels of ACh may augment antinociceptive effect as a result of axonal conduction block from spinal bupivacaine. Such an additive effect has previously been reported. In our study, the more rapid onset and spread of anaesthesia, as measured by the level of sensory block at 5 and 10 minutes, was significantly earlier after
spinal bupivacaine when combined with spinal neostigmine. At the same time, the increased duration and quality of analgesia for group III patients compared with group I values, revealed an additive effect of the combined administration of intrathecal neostigmine and bupivacaine.

Hypotension and bradycardia are common side effects of spinal anaesthesia, and they represent normal physiologic responses to anaesthetized spinal sympathetic nerve fibers. The primary physiologic alteration is decreased preload, which combines with bradycardia to reduce arterial blood pressure and cardiac output. Mild hypotension or bradycardia may be treated with volume expansion, ephedrine, or atropine. However, severe and/or rapidly progressing bradycardia demands aggressive treatment with epinephrine, followed by cardiopulmonary resuscitation if appropriate.

In our study, the difference in incidence of Intraoperative hypotension and bradycardia between the three groups was not significant, i.e. addition of neostigmine to bupivacaine (in group II and III) did not increase significantly the incidence of intraoperative hypotension and bradycardia than that which was recorded in group I (bupivacaine only).

To minimize the effect of sudden sympathetic block, a preload of 500 ml of normal saline was completed prior to instituting the block in our patients. Some recent studies suggested that intravenous prehydration does not prevent hypotension, but may reduce its incidence, irrespective of the volume infused or of the use of colloids versus crystalloids (100)(101).

Gradual heart rate reduction that stabilizes within 10% to 15% of baseline and is not associated with hypotension requires careful observation but may not require treatment. Similarly, 15% to 20% reduction of arterial blood pressure in healthy patients without pre-existing hypertension, coronary artery disease, or aortic stenosis is not necessarily associated with compromised end-organ blood flow. Intrathecal Injection of the drugs was given slowly to avoid development of severe hypotension, as one study
concluded that a 2 ml/min injection rate might be a simple and effective way to reduce the incidence and severity of hypotension during caesarean section under spinal anaesthesia. In our study, those who developed hypotension were managed by increase the rate of normal saline infusion with incremental doses of ephedrine and those who developed bradycardia were given atropine. Postoperative hypotension and bradycardia was not recorded in any patient of the three groups.

Neostigmine preparations used in the patient study included methyl- and propyl-parabens as preservatives. Early experimental and clinical trials used preservative-free Neostigmine.\(^{102}\) Although preservative-free is not associated with neurotoxicity, it is no longer marketed. Two investigations have confirmed that chronically administered intrathecal neostigmine containing methyl- and propyl-parabens in glucose-containing solution is not associated with any behavioral, chemical, or histopathological evidence of neurotoxicity.\(^{102}\) Tan and co-workers in the subsequent outpatient follow-up reviewed neurological sequelae, including persistence paraesthesia, sensory or motor deficits, and bowel or bladder dysfunction. None of the patients in that study developed short- or long-term neurological impairment or deficit during a 1-year follow-up period.

Despite its proven analgesic effectiveness, neuraxial neostigmine is not yet a widely accepted analgesic modality in clinical practice and continues to be an off-label indication. This is mainly because of the frequent incidence of nausea and vomiting. In a dose-response study, an intrathecal neostigmine dose, range of 6.25 – 50 µg, was associated with a relatively frequent incidence of nausea (33% - 67%) and vomiting (17% - 50%).

Reducing the dose to 10µg, the injection of neostigmine in a hyperbaric dextrose solution, and maintaining the patient in head-up position in patients receiving spinal neostigmine are effective measures in reducing the incidence of nausea and vomiting. This was explained by minimizing cephalad spread
and, presumably, subsequently reduces the incidence of nausea and vomiting. Probably the epidural route of administration of neostigmine may eventually prove superior to the intrathecal route with respect to the incidence of associated nausea and vomiting.\textsuperscript{(103)(104)}

In present study, we also observed a significantly higher intraoperative VAS-nausea and increased incidence of vomiting associated with intrathecal neostigmine at doses of 50 µg or 100 µg, in a dose-dependent manner with a significant number of patients requiring treatment. Maximum episode of nausea and vomiting occurred at 115 ± 63 min and at 63.7 ± 37 min in group II and III patients, after the study drug injection and this is consistent with previously reported delay of 60 – 120 min in the onset of nausea and vomiting after spinal administration of Neostigmine.\textsuperscript{(105)} This adverse effect is probably caused by the migration of neostigmine to the brain stem, because the nausea and vomiting did not occur until 63 – 115 min after spinal drug administration. None of the patient had abdominal cramps

In our study, we selected relatively low doses of neostigmine (50 and 100 µg) in hyperbaric bupivacaine solution and we maintained the patient in a head-up posture after the injection of the hyperbaric solution, in order to decrease the prevalence of adverse effects. In agreement with Hood's and Tan observations, metoclopramide used in our study was ineffective in stopping the nausea or vomiting. Three of five patients (60%) in group II and three of four patients (75%) in group III failed to respond to metoclopramide, and needed supplementation by another antiemetic agent, intravenous Ondansetron (4mg). Previous studies have reported similar difficulty in preventing or treating nausea and vomiting with spinal Neostigmine.

Intrathecal neostigmine can cause motor weakness of lower extremities in animals and humans volunteers by an ACH-mediated reduction in the motor neuron outflow. The addition of 50 µg neostigmine prolonged motor block from bupivacaine anaesthesia. In our study, the motor block produced
by intrathecal bupivacaine was greatly prolonged by the addition of 100 µg neostigmine. The duration of motor block increased from 4.8 ± 1.9 h with 50 µg neostigmine to 5.8 ± 1.6 h with a dosage of 100 µg neostigmine compared to the non-neostigmine group, 4.37 ± 1.5 hours.

Neostigmine-enhanced motor block from spinal local anaesthetics may be useful in some kinds of surgery, e.g. lower extremity surgical procedures requiring muscle relaxation.

Respiratory depression and pruritus ascribed to use of spinal opioids were not encountered with spinal neostigmine. There was no significant alteration in BP and heart rate in any of the patients. This is consistent with the work of other investigators, on the used of spinal neostigmine in human. Urinary retention has been observed with spinal intrathecal neostigmine, albeit the duration of urinary retention is brief compared with spinal morphine. We could not evaluate this parameter, in this study, as most of the patients were catheterized in the postoperative period.

One patient from group II (5%) and another patient from group III (5%) had intraoperative bowel movement 150 min and 120 min, respectively, after the spinal injection. However, this adverse effect has been reported by Gabriela et al. study.

In our study, dizziness, sedation and anxiety were not observed in patients received intrathecal neostigmine, as was reported by Hood's et al. in patients receiving 750 µg dose, and this can be explained by the smaller dose (50 – 100 µg) used in our study. (79)
CONCLUSIONS

• Addition of neostigmine improves the onset of bupivacaine, as measured by the level of sensory block and this reveals an additive effect of the combined administration of intrathecal neostigmine and bupivacaine.

• In patients undergoing infra-umbilical surgery, intrathecal neostigmine administered at 50 µg or 100 µg enhances the effects of bupivacaine anaesthesia and provides dose-dependent analgesia for a period of about 4.5 – 7.5 hours.

• Spinal neostigmine prolongs the duration of motor block from bupivacaine anaesthesia, which may be useful in some kinds of surgery. On the other hand, this can limit its use for day case surgery.

• This anaesthetics mixture, however, especially that containing neostigmine at 100 µg, causes a significant increase in adverse effects, such as nausea and vomiting, and prolongs motor block, which may restrict the usefulness of intrathecal neostigmine as a sole analgesic agent.

• A part from nausea and vomiting, this regimen of spinal neostigmine and bupivacaine is not associated with any serious side effects.

• Metoclopramide, used in our study, is effective in decreasing the severity of nausea but is ineffective in stopping vomiting when compared with the effectiveness of Ondansetron.

• The technique is simple, instruments needed are readily available and no special drug preparation is needed (as it is safe to use neostigmine with preservative).
RECOMMENDATIONS

As has been demonstrated by this, and previous, studies intrathecal neostigmine could produce a dose-dependent analgesia and a dose-dependent adverse effect. Therefore, efforts can be made to reduce the undesirable adverse effects of intrathecal neostigmine to be clinically useful, we recommend:-

• Minimization of cephalic spread, which is blamed for the increases incidence of nausea and vomiting. The mixture of neostigmine with hyperbaric dextrose solution of spinal anaesthetic is advocated.

• Probably the epidural route of administration of neostigmine is minimizing cephalic spread and may eventually prove superior to the intrathecal route with respect to the incidence of associated nausea and vomiting.

• A mixture of spinal Neostigmine, opioids, and local anaesthetic, can increase the duration of analgesia, and reduce the postoperative analgesic demand without increasing the incidence of adverse effects. As the mass of each agent will be decreased.

• **Prophylactic** administration of the antiemetic agent, ondansetron, may be more effective than treatment, for prevention of intra- and postoperative nausea and vomiting.

• Because the better quality of analgesia increases the incidence of untoward side effects, a larger sample should be studied before this application can be routinely used clinically.

• Regional anaesthesia for caesarean section, whether urgent or elective, has become the anaesthetic technique of choice. In previous studies, Intrathecal neostigmine did not affect fetal heart rate tracing or apgar scores in women prior to cesarean section and was well tolerated. Intrathecal neostigmine was associated with reduced postoperative morphine requirements with a trend toward blunting of lidocaine-induced
hypotension. These findings support further clinical investigation of intrathecal neostigmine in obstetrics.
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Date: / / Patient number ( )

Name: ........................................................................................................
Age: (22-70y) ( y)
Sex: (M) (F)
Place (KTH) (SUH) Ward: ..................................................

Kind of surgery:
Surgery duration: min

History:
- Any systemic disease (Y) (N) .........................................................
  ........................................................................................................
- Presence of preoperative nausea or vomiting (Y) (N)
- Any premeditation (Y) (N)
- Written informed consent (Y) (N)
- Any CI to spinal anaesthesia (Y) (N)

Examination finding:
Preload 500 ml – normal saline 0.9 (Y) (N)
Intra-operative total fluids ( ml)

Test drug given:
- Group1 (bupivacaine 15mg + 0.5ml D5%) ( )
- Group2 (bupivacaine 15mg+0.5ml neostigmine 50µg) ( )
- Group3 (bupivacaine 15mg+0.5ml neostigmine100µg) ( )

ASA physical status (1) (2)

Time of start of anaesthesia ( )

Time of start of operation ( )

Time of end of operation ( )

Sensory level at:
- 5 minutes ( )
- 10minutes ( )
<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Atropine 0.5mg iv</th>
<th>Ephedrine 5mg iv</th>
<th>Vomiting number</th>
<th>Nausea (VAS) (0-10)</th>
<th>Sedation (VAS) (0-2)</th>
<th>Pain (VAS) (0-10)</th>
<th>Motor Brom. scale (2)(time)</th>
<th>Diclofenac 75mg IM</th>
<th>Metoclopramide 10mg IV</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ward</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Note:

- atropine 0.5mg IV if PR ≤ 60 beats/min
- ephedrine 5 -10mg IV if systolic BP ≤ 100 mmHg
- nausea (VAS) >2

- vomiting > once
  - Metoclopramide 10 mg i.v.

- Diclofenac 75mg IM if pain score ≥ 4 (repeated 8 hourly if necessary).

- Objective score of sedation based on eye opening:
  - Eyes opening spontaneously = 0
  - Eyes opening in response to speech = 1
  - Eyes opening in response to physical stimulation = 2

- Bromage motor scale:
  - No block (1) (the ability to flex the knees and feet)
  - Partial block (2) (ability to flex the knees and resist gravity with full movement at the feet)
  - Almost complete block (3) (inability to flex the knees but retain the ability to flex the feet)
  - Complete block (4) (in ability to flex the legs or feet).