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Comparative study between the effect of different additives to caudal anesthesia in pediatrics on postoperative pain

Thesis

Submitted For Fulfillment of M.D. Degree
In Anesthesia and ICU
By

Mahmoud Ibrahim Abd El-fattah
M.B., B.cH, MSC in Anesthesia and ICU
Faculty of Medicine, Benha University.

Supervisors

PROF. DR. Saad Ibrahim Saad
Chairman &Professor of Anesthesia and ICU

Faculty of Medicine, Benha University.

PROF. DR. Reda Khalil kamel
Professor of Anesthesia and ICU

Faculty of Medicine, Benha University.

ASSIST. PROF. Ehab Said Abd El-Azeem
Assist. professor of Anesthesia and ICU

Faculty of Medicine, Benha University.

Benha Faculty of Medicine

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Mahmoud Ibrahim

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Introduction

The pain model, developed by Descartes in the 17th century, which focused entirely on tissue damage (nociception), held well until the 20th century. In the mid 1960s, the concept of pain became more comprehensive. Due to the increasing awareness of the relationship between the mind and the body regarding pain perception, a new theory for pain was proposed. A Canadian professor, Melzack, together with Wall created this Gate-Control Theory (GCT). This theory emphasizes on the complex interplay between the central nervous system (CNS) and the peripheral nervous system (PNS). According to **(Melzack and Wall., 1965)** only certain pain-messages are permitted to pass through to the brain, in other words, "nerve gates" determine the degree to which an individual receives a pain sensation. This theory is connected to the principle that various CNS activities can play a meaningful role in sensory perception. Particular activities such as attention, emotion, and memories concerning previous experience with the event are factors that influence the new sensation. Since this revolutionary discovery on pain physiology, many groups have proposed integrated definitions of pain perception ***(Gold et al., 2006).***

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Pain is the most common reason for seeking health care. It occurs with many disorders, diagnostic tests, and treatments. Though pain is not a disease, rather a symptom, it disables and distresses more people than any single disease. The

physical responses to pain such as tachycardia, hypertension, tachypnea, pallor, diaphoresis, mydriasis, hyper vigilance and increased muscle tone are related to the stimulation of the autonomous nervous system. However, using physiologic signs to indicate pain is unreliable, for they could be caused by a number of other reasons ***(Smeltzer & Bare, 2004).***

A child's pain does not influence only the child, but also the family. The involvement of the parents in the pain assessment and management process is important. Families can be a source of support for children in postoperative pain. The child's pain also increases stress in the family members. Nevertheless, more attention should be paid on parents' needs and on their counseling about children's pain in clinical pediatric nursing ***(Kankkunen et al. 2004).***

Pain being a subjective and complex in its nature, the intensity of pain is then primarily assessed through self-report in both adults and children ***(Merkel & Malviya, 2000)***.

A child's ability to express or report pain is dependant on his/her physical and psychological developmental stage. One should never underestimate a child's report of pain, though a child may not be able to specify his/her feelings and pain experience ***(Salanterä et al. 2006).***

It is challenging to assess pain through self-report with small children due to their lack of ability to communicate verbally. The vocabulary of these small children under school-age is rather curt. In addition, a small child may not have experienced a lot of pain, and therefore might find it difficult to express pain with fitting terms. The scales may be too abstract for them. This is why in the assessment of pain in smaller children different face-scales have become generally used. The only problem that seems to appear with these face-scales is that small children tend to mix up pain and feelings, such as fear, anger or irritation. In any case, when a child reports pain, it should be taken seriously, and the cause of pain should be determined ***(Salanterä et al. 2006).***

Aim of the study

To study if the adjuvant drugs added to caudal anesthesia like (dexmedetomidine, fentanyl or clonidine) have a beneficial effect on post operative pain relief and in reducing the rescue demand of analgesics for pediatric patients undergoing minor subumblical surgery.

CAUDAL ANESTHESIA

Caudal epidural block (CEB) is one of the most preferred pediatric regional anesthesia methods for infants and children who need operations under umbilicus level, for example urogenital, rectal, inguinal, lower extremity surgeries. CEB is relatively easy to perform and provides efficient analgesia for both intraoperative and postoperative period. Although there are some studies which report caudal anaesthesia as the sole anaesthetic method in particular cases for infants and children, caudal anaesthesia is still combined with general anaesthesia for most of the cases***(Brenner et al., 2010)***.

Caudal blockade can be a safe and effective analgesia technique in suppressing some elements of the hormonal stress response. Caudal block, in combination with light general anesthesia, may be useful inpremature children, those with comorbidity, as well as those with specific medical diseases such as cardiac disease or muscular atrophy. However, the risks and benefits of caudal epidural blockade must be considered on an individual basis ***(Johr& Berger, 2004)***.

Stress responses to surgical insult and postoperative pain elicit changes in hormonal secretion. Surgery is associated with metabolic and endocrine responses characterized by hyperglycemia, an increase in adrenocorticotropic hormone, cortisol, prolactin, antidiuteric hormone, growth hormone, catecholamines, angiotensin II, aldosterone, glucagons, IL-1 and lactate, and a decrease in insulin and testosterone. Epidural analgesia inhibits the metabolic and endocrine stress responses associated with lower abdominal surgery. However, general anesthesia does not

inhibit these responses. Caudal anesthesia has been used for surgery and postoperative pain relief in children. The aim of this study was to compare the concentrations of metabolic variables and hormones during and after surgery utilizing general anesthesia, with or without caudal block in children***(Bozkurt et al., 2000).***

Caudal epidural block is a commonly performed procedure in pediatric age group. It offers excellent analgesia without the side effects of intravenous opioid medications, viz. nausea, sedation, and respiratory depression. Caudal blocks are generally performed after induction of general anesthesia in children. Traditional teaching relies on the subjective sensation of "give" or "pop" felt by the operator as the advancing needle pierces the sacrococcygeal ligament and the lack of resistance to injection of the local anesthetic. Although the block is easily performed, the success rate is less than 100% and varies with the experience of the operator. Objective parameters of successful caudal needle placement will increase the success of the block. In a large teaching hospital such as ours, with a number of residents in training, additional methods to predict correct needle placement would increase accuracy.

Several studies have evaluated the accuracy of parameters to predict correct caudal needle placement. These include an audible "swoosh" on auscultation over the lower back during injection, a reduction in heart rate during drug injection and a lax anal sphincter at the end of the procedure. This study was undertaken to compare the sensitivity, specificity, positive predictive value, and negative predictive value of the following predictors of successful caudal block, viz. swoosh test, heart rate reduction during injection, and laxity of anal sphincter following procedure***(Krishna et al., 2004).***

Anatomical Considerations

Significant anatomic differences in comparison with adults, should be considered while utilizing regional anesthesia in children. For instance, in neonates and infants, the conus medullaris is located lower in the spinal column (at approximately the L3 vertebra) compared to adults where it is situated at approximately the L1 vertebra. This dissimilarity is a result of different rates of growth between the spinal cord and the bony vertebral column in infants. However, at approximately 1 year of age the conus medullaris reaches similar L1 level as in an adult. The sacrum of children is also more narrow and flat compared to the adult population. At birth, the sacral plate, which is formed by five sacral vertebrae, is not completely ossified and continues to fuse until approximately 8 years of age. The incomplete fusion of the sacral vertebral arch forms the sacral hiatus. The caudal epidural space can be accessed easily in infants and children through the sacral hiatus. Due to the continuous development of the sacral canal roof, there is considerable variation in the sacral hiatus. In children, the sacral hiatus is located more cephalad compared to adults. Therefore, caution is warranted when placing caudal blocks in infants as the dura may end more caudad thereby increasing the risk of accidental dural puncture. It has also been suggested that the epidural fat is less densely packed in children than in adults. This loosely packed epidural fat may facilitate not only the spread of local anesthestic, but it may also allow the unimpeded advancement of epidural catheters from the caudal epidural space to the lumbar and thoracic level ***(Igarashi et al., 1997).***

Clinical Pearls

- In the neonate the intercristal line bisects L5 (cf L4 or L3/4 interspace in the adult) and the spinal cord ends at L3 in first year of life (cf L1 in the adult).
- As a general rule the epidural space will be found at 1 mm/kg of body weight, however, there is considerable individual variation.

Indications

Caudal blocks have been shown to reliably block dermatomes below the level of the umbilicus (T10–S5) in children < 20 kg (6 yr of age). It is therefore suitable for all types of surgery below the umbilicus in these children (e.g. inguinal herniotomy, orchidopexy and hypospadias repair). In older children, only sacral dermatomes are reliably blocked. Peripheral nerve (e.g. ilioinguinal) or compartment (e.g. rectus sheath) blocks may be more beneficial in these children ***(Tou et al., 2001).***

Technique

All regional blocks should be performed using an aseptic tech-nique. The most reliable method of identifying the sacral hiatus appears to be by identifying the posterior superior iliac spines. The thumb and middle fingers of the operator's hand are placed on the posterior superior iliac spines and the index finger is then used to complete an equilateral triangle, thus identifying the sacral cornua and hiatus. A 20 or 22 G i.v. cannula is most commonly used for this block because: (i) the needle acts as an obturator and prevents seeding of skin into the epidural space; (ii) a more definite give is produced on passing through the sac-rococcygeal membrane and the advancement of the cannula over the needle helps to confirm correct placement; (iii) the soft can-nula is less likely to puncture a vessel or dura and, because of its size, it is more likely to confirm i.v. or

subarachnoid placement; (iv) any resistance encountered during injection of the local anaes-thetic indicates incorrect placement; and (v) the cannula allows the placement of an epidural catheter, if desired***(Rowney &Doyle, 1998).***

Anatomy

The caudal epidural space is the lowest portion of the epidural system and is entered through the sacral hiatus. The sacrum is a triangular bone that consists of the five fused sacral vertebrae (S1- S5). It articulates with the fifth lumber vertebra and the coccyx.

The sacral hiatus is a defect in the lower part of the posterior wall of the sacrum formed by the failure of the laminae of S5 and/or S4 to meet and fuse in the midline. There is a considerable variation in the anatomy of the tissues near the sacral hiatus, in particular, the bony sacrum. The sacral canal is a continuation of the lumbar spinal canal which terminates at the sacral hiatus. The volume of the sacral canal can vary greatly between adults.

The sacral canal contains:

1. The terminal part of the **dural sac**, ending between S1 and S3.

2. The five sacral nerves and coccygeal nerves making up the **cauda equina**. The sacral epidural veins generally end at S4, but may extend throughout the canal. They are at risk from catheter or needle puncture.

3. The **filum terminale** - the final part of the spinal cord which does not contain nerves. This exits through the sacral hiatus and is attached to the back of the coccyx.

4. **Epidural fat**, the character of which changes from a loose texture in children to a more fibrous close-meshed texture in adults. It is this

difference that gives rise to the predictability of caudal local anaesthetic spread in children and its unpredictability in adults.

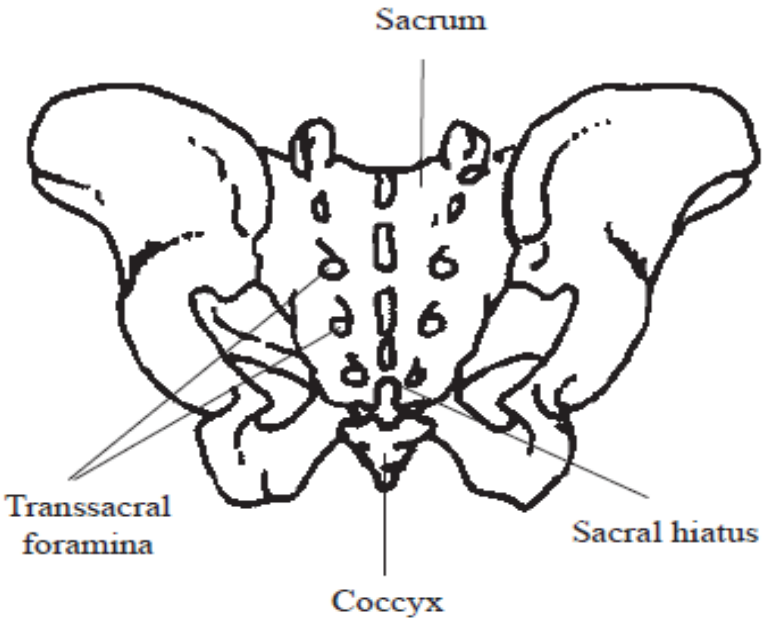


Fig. 1. *Anatomy of the sacrum and coccyx*
(Senoglu et al., 2005)

Anatomical landmarks (Figure 1)

The sacrum is roughly the shape of an equilateral triangle, with its base identified by feeling the two posterosuperior iliac processes and a caudal summit corresponding to the sacral hiatus. The sacrum is concave anteriorly. The dorsal aspect of the sacrum consists of a median crest, corresponding to the fusion of sacral spinous processes. Moving laterally, intermediate and lateral crests correspond respectively to the fusion of articular and transverse processes. The sacral hiatus is located at the caudal end of the median crest and is created by failure of the S5 laminae

to fuse (Figure 2). The hiatus is surrounded by the sacral cornua, which represent remnants of the inferior S5 articular processes and which face the coccygeal cornua. Palpation of the sacral cornua is fundamental to locating the sacral hiatus and to successful caudal block.

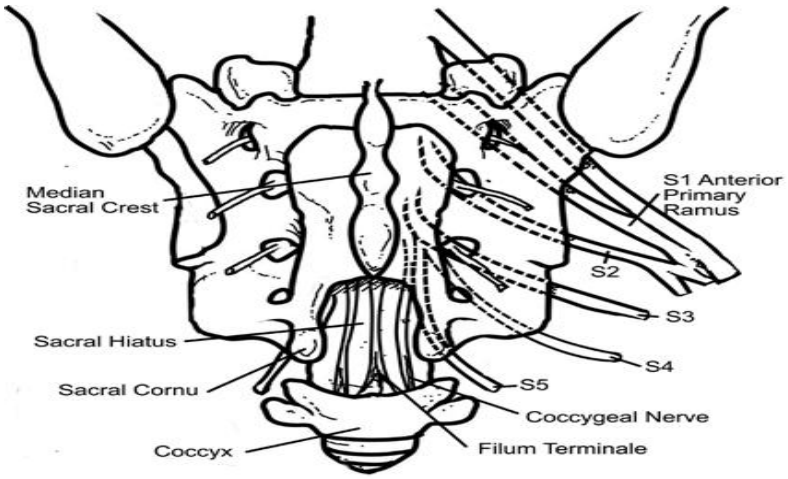


Fig. 2. *The posterior aspect of the sacrum and sacral hiatus*

(Senoglu et al., 2005)

The sacral hiatus is the shape of an inverted U, and is covered by the sacro-coccygeal ligament, which is in continuity with the ligamentum flavum. It is large and easy to locate until 7-8 years of age. Later, progressive ossification of the sacrum (until 30 years old) and closing of the sacro-coccygeal angle make its identification more difficult. Note that anatomical anomalies of the sacral canal roof are observed in 5% of patients and this can lead to unplanned cranial or lateral puncture.

The sacral canal

The sacral canal is in continuity with the lumbar epidural space. It contains the nerve roots of the cauda equina, which leave it through anterior sacral foraminae. During CA, leakage of local anaesthetic agent (LA) through these foraminae explains the high quality of analgesia, attributable to diffusion of LA along the nerve roots. Spread of analgesia

cannot be enhanced above T8-T9 by increasing injected LA volume. The dural sac (i.e. the subarachnoid space) ends at the level of S3 in infants and at S2 in adults and children. It is possible to puncture the dural sac accidentally during CA, leading to extensive spinal anaesthesia. Therefore the needle or cannula must be cautiously advanced into the sacral canal, after crossing the sacro-coccygeal ligament. The distance between the sacral hiatus and the dural sac is approximately 10mm in neonates. It increases progressively with age (>30mm at 18 years), but there is significant inter-individual variability in children**.** The contents of sacral canal are similar to those of lumbar epidural space, predominantly fat and epidural veins. In children, epidural fatty tissue is looser and more fluid than in adults, favoring LA diffusion***(Dalens, 2002).***

Indications

i. Whenever possible all children should receive RA in some form or other, appropriate to the proposed surgery.

ii. RA in children is usually administered and practiced after induction of general anaesthesia except in certain situations like, premature baby or ex-premature baby up to a conceptual age of 60 weeks when there is fear of post operative apnoea. It is a well-recognized fact that the incidence of post operative apnoea is least under spinal block as compared to spinal with sedation or general anaesthesia. Whatever technique is practiced in this group of infants proper monitoring is a must.

iii. Children undergoing thoracic and upper abdominal surgeries those need aggressive pain management in the post-operative period***(Sartorelli et al., 1992).***

Contra indications

a. Lack of parental consent

b. Infection at the site of administration of the block

c. Any coagulation disorder.

Common regional analgesia techniques

The most commonly practiced RA technique is the caudal (epidural) block. Other common blocks are ilioinguinal ilio hypogastric block (hernia) and block of the dorsal nerve of penis (penile) ***(Fortuna., 1967).***

The technique

The approach to the hiatus should be made from above along the sacral spines and not from the tip of the coccyx. That makes it easy to identify the commonly seen sacral anomalies in children.An imaginary line is drawn between the two posterior superior iliac spines. They can be identified as projections or dimples in chubby kids (fig.3).

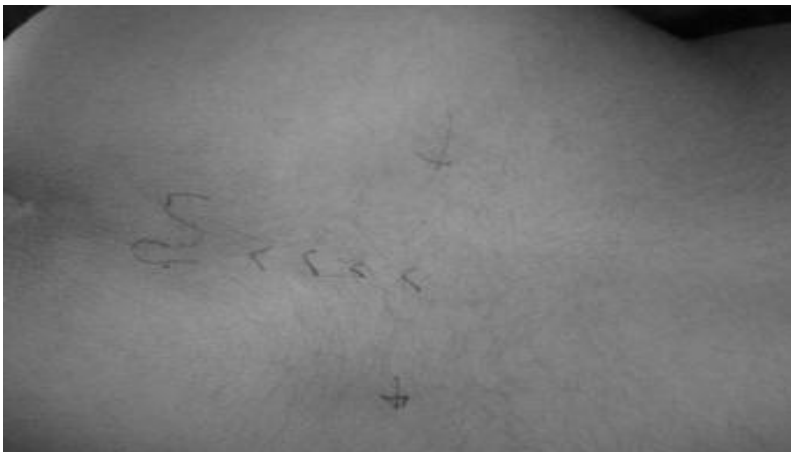


Fig. 3 : *Surface anatomy of sacral hiatus in relation to sacral spines*.

This line passes through the S1-S2 space or S2 spine. Feel the S2 spine and proceed downwards feeling the spine of S3, S4 till one feels the hiatus. The hiatus might be at the level of any of these spinous processes. At higher level chance of puncturing the dural sac is a possibility. Once the hiatus is identified by the thumb, it is moved across to feel the laminae. Then the skin is pulled up to the spinous process (the point of

injection is not touched). This way there is a overlap between the site of puncture of skin and the ligament, preventing any leakage of the drug administered. A 22/23 G hypodermic needle is advanced at an angle of 70-90o at the apical region of the hiatus (fig.4). The ligament can be identified by the loss of resistance or the 'pop' of overcoming the resistance. The saccro coccygeal ligament is always felt.

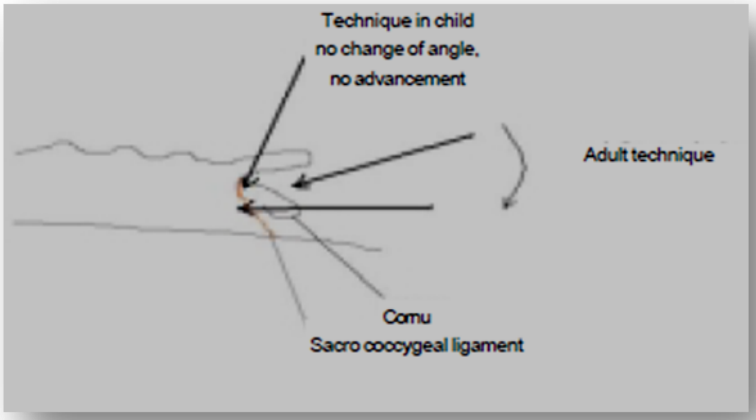


Fig. 4 : *Technique of caudal block in children and adults.*

Once the needle crosses the ligament, it should be stopped and drug deposited. Further advancement or change of direction is not necessary. In case thinner needles are used it should be disconnected from the syringe to look for any back flow. The negative pressure generated by aspiration often collapses the vein over the needle tip. Some people advice routine use of styletted needle for fear of introducing dermal plug. However it has been seen that microscopic plugs or cells is not possible to avoid even in a 26,27G styletted needle. Some people advocate routine use of test dose. However we do not practice it and have not had any complication in our practice of last over twenty years.

Catheter insertion

In patients where post operative pain relief is necessary for longer duration a catheter might be inserted through the caudal space and advanced to the dermatomes involved in incision. An infusion with more lipophilic drug like fentanyl is used. When the catheter is left at the caudal epidural space only hydrophilic opioid like morphine can be used intermittently. It is effective even for thoracic and upper abdominal surgery.

Catheter can be inserted through a Touhy needle (fig.5). The length of catheter to be advanced has to be measured prior to insertion. It can also be inserted through an indwelling cannula.

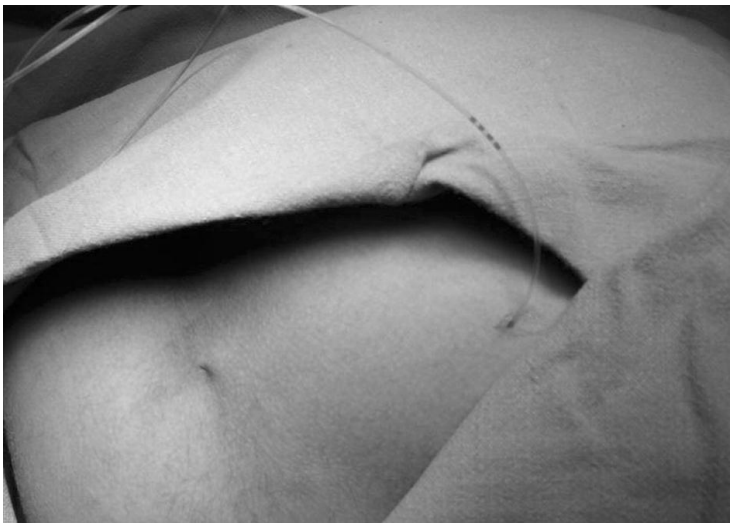


Fig. 5 : *Tunneling of caudal epidural catheter.*
(Pegues et al., 1994).

An 18 G catheter easily passes through 18 G cannula. The possibility of catheter not reaching or kinking or knotting is very high. Hence one should try to confirm the tip radiologically using a water-soluble dye. As the sacral hiatus is close to the anus there is possibility of contamination of the catheter and the puncture site. It can be prevented by occlusive dressing with a water resistant flap cover or by bringing out the catheter on the lateral flank by subcutaneous tunneling. The 18G catheter has less

chance of kinking than 20G/22G ones. The catheter advancement from caudal route has less chance of kinking than through the lumbar route.

Techniques

- **‘‘Single-Shot’’ Caudal Block**

The single-dose or ‘‘single-shot’’ caudal technique is the most commonly used neuraxial block for children. Developmental anatomy contributes to the ease of caudal needle placement and, therefore, the popularity of the technique in young children compared with adults, for example, shows that prepubertal children have less presacral fat, making identification of the bony landmarks easier. Additionally, in children, the sacral ligament is noncalcified and the hiatus is wide, further contributing to the ease of caudal needle placement. Caudal block is a useful adjunct to general anesthesia in most procedures performed below the umbilicus. In larger volumes (1–1.25 mL/kg) and in younger children, it has been described for use in upper abdominal and lower thoracic procedures. It is the authors’ experience, however, that analgesia is less reliable for procedures at this higher level. It is less commonly used as the sole anesthetic technique, but has been described as an alternative to spinal or general anesthesia for herniorrhaphy in preterm infants***(Henderson et al., 1993).***

Techniques

With the patient in the lateral decubitus or prone position with a pillow under the pelvis, the area of entry is sterilely prepped with betadine. Commonly a short 20 or 22 gauge beveled needle is advanced at a 45° to 90° angle at the level of the sacrococcygeal ligament into the skin (Figure 1).

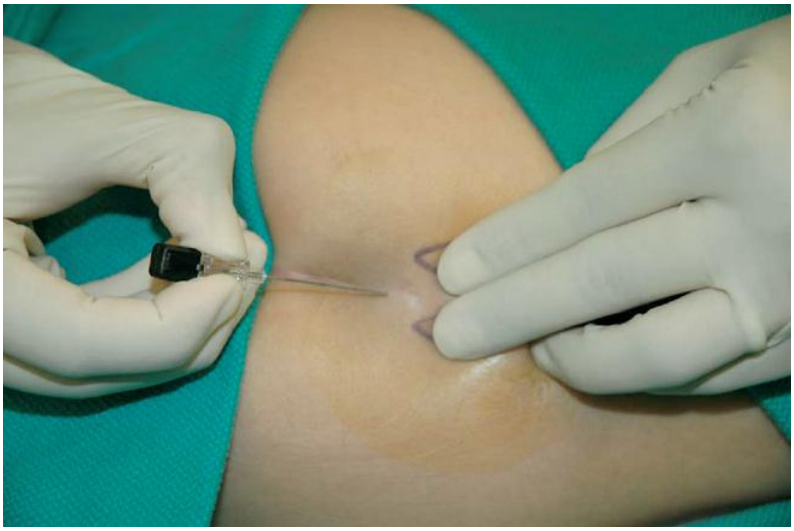


Fig. 6. *Caudal needle placement*. The sacral cornu is identified(blue marks); a styletted needle is placed between the cornu and is advanced until a loss of resistance is perceived. The stylet is removed, and the local anesthetic solution is injected after a test dose in graduated increments. A total volume of 1 mL/kg is used.

The needle will traverse the dermis followed by subcutaneous tissues. Once the "pop" or loss of resistance through the sacrococcygeal ligament is felt, the angle of the needle is decreased to approximately 30° and is advanced a few millimeters. This advancement assures complete insertion of the tip of the needle, including the bevel into the sacral canal. However, too much advancement of the needle can cause penetration into the dura, so care should be taken to prevent this. The allowed distance that the needle can be advanced depends on age of the child as well as normal variations in the ending of the dural sac.

After entry into the caudal epidural space through the sacrococcygeal ligament, a single injection of local anesthetic with or without other medications is commonly done.

The type of needle used for the caudal is not as important as the test that you choose to confirm your needle is in the epidural space. Smaller needle may bend on entry through the skin, making it hard to find and feel the loss of resistance across the ligaments. Furthermore, smaller

needles may make accidental dural or venopuncture difficult to ascertain***(Dalens, 2002).***

Aside from a needle, as described above, an angiocath can also be inserted with the technique described. A 22- or 20-gauge angiocatheter is used, but a 45° entry point is used to prevent kinking of the catheter once the catheter is ad vanced over the needle. As above, the loss of resistance is felt, the angle is decreased, and the needle is advanced a few millimeters. With the needle stabilized, the catheter is fed off of the needle into the epidural space.

Many different techniques are used to further confirm proper placement of the needle as well as the injectate solution. The absence of subcutaneous bulging of tissues and the lack of resistance with injection of local anesthetic are some common signs used to assure proper needle placement. Alternatively, a description of the whoosh versus modified swoosh is described by injecting 1 mL of air or saline, respectively, while listening with a stethoscope over the lower lumbar spine. If a "swoosh" or "whoosh" sound is heard, there is a 96% positive predictive value that one is in the proper place. However, there is no statistical significant difference between clinical predictors stated above and the "whoosh" or "swoosh" technique. The risk with the "whoosh" technique (air injection) is that of venous embolism and a patchy block. However, if saline or local anesthetic is used, the risk of air embolism is diminished with the caveat of possible dilution of the local anesthetic with saline***(Talwar et al., 2006).***

Ultrasound is another technique used to confirm placement of the needle in the epidural space. Nerves can be hyperechoic or hypoechoic depending on the size of the nerve and the angle of the ultrasound beam. Therefore, on a cross-sectional view of a nerve, the hypoechoic region

can be the nerves, whereas the hyperechoic region can be the connective tissue or vice versa.

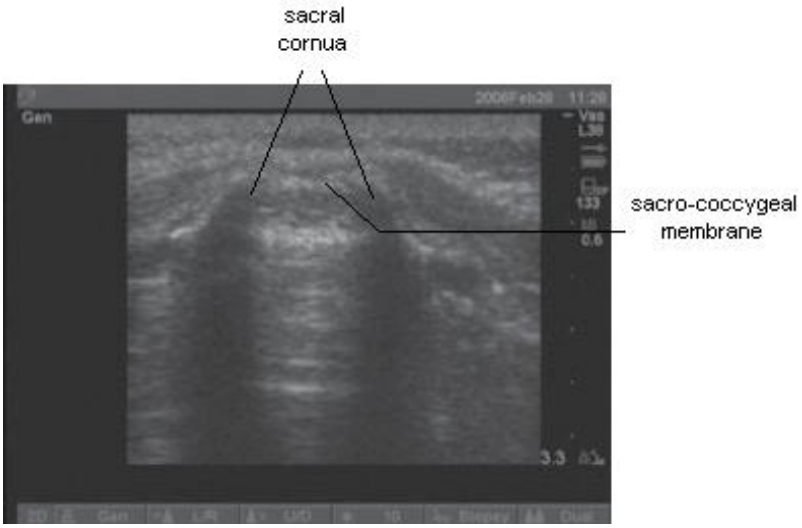


Fig. 7. *Ultrasound detection of caudal space*

An advantage of ultrasound guidance in pediatrics is the direct imaging of the structures and being able to observe the proximity of the needle to those surrounding structures to prevent damage to them***(Marhofer & Frickey, 2006).***

Ultrasound can allow visualization of the intrathecal structures, the dural sac, the epidural space, and the cauda equine. Also, direct visualization of the injection of local anesthetic can be seen in real time. However, ultrasound imaging can be difficult due to ossification of the vertebral column but can be accomplished. More recently, ultrasound has been suggested to help sacro-coccygeal hiatus location and to visualize isotonic serum or LA injection into sacral epidural space (Figures 7 and 8)***(Raghunathan et al., 2008).***

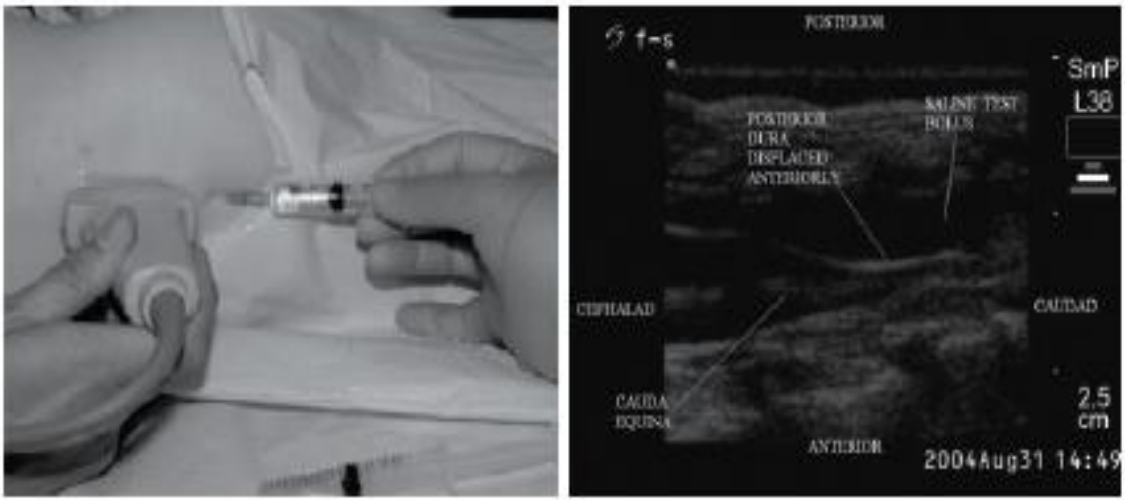


Fig. 8. *Ultrasound detection of caudal space*

These authors have also outlined the interest in ultrasound control within the context of learning the technique, rather than for use in standard practice. Despite the difficulty, ultrasound can be used to visualize the tip of a needle in the epidural space as well as the advancement of a catheter in the epidural space in very small infants. In a study of 35 preterm infants, all of the neural structures could be seen because of the incomplete ossification of the vertebral column. One could see the spread of local anesthetic in the epidural space in a longitudinal view of the structures. The biggest advantage they saw of ultrasound was being able to identify actual epidural puncture and subsequent advancement and final placement of the tip of the catheter. Real-time viewing of the needle also allowed direct vision of the tip of the needle to avoid damage to surrounding neural structures***(Willschke et al., 2007).***

Electrical stimulation is yet another technique used to confirm needle placement. Tsui describes the anal sphincter stimulation using an insulated needle. With nerve stimulation of 1-10 mA at 1 Hz, contraction of the anal sphincter causes an “anal wink” or anal sphincter contraction

reassuring with almost 100% certainty of epidural needle placement. However, an insulated needle needs to be used, which often may make it difficult to feel the loss of resistance once entering the sacrococcygeal ligament. Furthermore, these needles are not styletted and are more costly ***(Tsui et al.,1999).***

- **‘‘Catheters’’ Caudal Block**

Because the duration of analgesia of a single-shot caudal epidural is limited, catheters are often placed to allow prolonged intraoperative as well as postoperative analgesia. Multiple techniques are available for catheter placement: blind, ultrasound-guided, stimulating, and using electrocardiography. The caudal technique to access lumbar and thoracic epidural spaces is commonly used due to the risk of damage to the spinal cord with either direct insertion at those higher regions. The caudal technique is usually saved for children less than 1 year due to difficulty in passing the catheters in older children because of the increased lumbar lordosis that comes with age.

The blind catheter technique is similar to the blind single- shot caudal. A commercially available caudal catheter kit that includes a Crawford needle may be used, or an 18-gauge Angiocath® may be used to enter the epidural space. In the case of the Angiocath®, once it is felt that the needle is in the epidural space, the angiocath is advanced and the needle is removed. The styletted catheter is then measured along the spine from the sacrum to the desired level to estimate the proposed depth the catheter needs to be inserted. The stylette, once the catheter reaches the desired distance, is removed. The stylette is used to prevent caudal catheter coiling or kinking while passing it. If resistance is met, the patient is either extended or flexed or saline is injected to overcome the resistance***(Tobias et al., 1993).***

The tip of the catheter is then checked using multiple techniques to assure location. Radiographic confirmation may be the most ideal; however, due to time consumption in the operating room, other techniques are used. Ultrasound can help assess the actual distance of the catheter in the epidural space. Chawathe and colleagues showed that the catheter was visualized in the epidural space in children less than 6 months. Not only was the tip of the catheter visualized but the entire length of the catheter was seen. However, practice and precision is needed to visualize the catheter in relation to the other structures in 35 neonates***(Chawathe et al., 2003).***

Electrical stimulation is also used to confirm catheter placement. An advantage of the stimulating technique is that changes can be made while the catheter is actually being advanced as opposed to, after it is secured, the dermatome that the catheter tip is located usually being stimulated on advancement.

The caudal space is entered either using an Angiocath® or Crawford needle, and the catheter is then advanced to a desired level. As the catheter is advanced, an anode lead of an electrical stimulator is attached to an ECG patch and placed on the patient. The cathode lead is connected to the Johans adapter attached to the hub of the catheter. An electrical stimulus of 1-10 mA at 1 Hz is used to visualize twitching of the respective muscles as the catheter is advanced cephalad through the epidural space. For example, for a thoracic desired catheter, first lower limb muscle twitches were seen followed by abdominal/intercostals muscles as the catheter was advanced cephalad. Using different voltages, one can decipher whether the catheter is epidural, subarachnoid, subdural, or close to a nerve. One will see muscle twitching at 1-10 mA, 0.2 mA, 0.3 mA, and 0.5 mA for the respective locations***(Wagner et al., 2005).***

Electrocardiography is another way to guide the catheter to a desired level. The catheter is set up the same way with the Johans adapter and inserted using either an angiocatheter or Crawford needle. The stylette is adjusted to be approximately 10 mm proximal to the tip of the catheter. A 5-lead ECG monitor is needed which will show leads II and III. The catheter is then flushed with saline and advanced, and the ECG is noted. As the catheter advances, the ECG will change until the two ECGs match, which indicates that the tip of the catheter is at the level of the ECG lead on the back. The main change in the ECG is the increase in the amplitude of the QRS complex as it comes closer to the heart. Tsui and coworkers were able to show in a study of 20 patients that they were able to place the catheter within two vertebral levels in the thoracic region***(Seal et al., 2002).***

COMPLICATIONS

Complications of CA are uncommon (0.7 per 1000 cases), are more likely if inadequate equipment is used and are more frequent in infants. If the technique fails it should be abandoned to avoid occurrence of potentially serious complications. Significant complications, in order of decreasing frequency, are:

• **Dural tap.** This is more likely if the needle is advanced excessively in the sacral canal when subarachnoid injection of local anaesthetic agent may cause extensive spinal anaesthesia. Under general anaesthesia this should be suspected if non-reactive mydriasis (pupillary dilation) is observed.

• **Vascular or bone puncture** can lead to intravascular injection and consequently LA systemic toxicity. Preventative measures are use of a

test dose, cessation of injection if resistance is felt and slow injection under hemodynamic and ECG monitoring. Sacral perforation can lead to pelvic organ damage (e.g. rectal puncture).

• **Exceeding the maximal allowed LA dose** risks overdose and related cardiovascular or neurological complications.

• **Delayed respiratory depression** secondary to caudally injected opioid.

• **Urinary retention** - spontaneous micturition must be observed before hospital discharge.

• **Sacral osteomyelitis** is rare (one case report)

(Wittum et al., 2003).

Local anesthetics(Bupivacaine)

Regional anesthesia (RA) can help significantly decrease side-effects in the pre- and postoperative period. Local anesthetics (LA) and opioids remain the most commonly used drugs in RA, via neuraxial or peripheral route, by single shot or continuous infusion. In clinical practice, however, physicians sometimes fail to consider properly the specific properties of a local anesthetic, its concentration, time of administration, side-effects and relative efficacy and potency as compared with other drugs. Besides LA and opioids, a wide range of other drugs has been assessed for neuraxial and peripheral administration to provide anesthesia and analgesia, either as adjuvants or because of recently discovered anesthetic properties. We reviewed the available literature to assess the properties and the indications of all drugs used in RA and provide an overview that can allow clinicians to pick the one that best suits the type of surgery to be performed and the anesthesia/analgesia desired***(Capdevila et al., 2008).***

Clinical pharmacology of Local anesthetics used in RA

All local anesthetics (LA) have potential neurotoxic properties at higher concentrations and may induce neuronal death. It is known that the higher the LA plasma levels the higher the risk of neural damage even if the newer LAs, ropivacaine and levobupivacaine, have reduced neurotoxic and cardiac side-effects ***(Foster and Markham, 2000).***

Long before the first clinical use of local anaesthetics, the native South Americans enjoyed the leaves of Erythroxylum Coca for its energizing and mood enhancing effects. It was not until 1860 in Germany, that the chemist Niemann isolated cocaine from erythroxylin extract. At the time

he noticed on tasting, that it caused the tip of his tongue to go numb. Its mood enhancing effects were soon noted and before long it was a constituent of many elixirs and beverages, the most famous of which was Coca-Cola***(Johnson et al., 2002).***

In 1884, Carl Koller discovered its potential for topical anaesthesia by applying a solution of the crystals to the surface of the eye. In the following years it was successfully used for infiltration, peripheral nerve blockade, caudal and spinal anaesthesia. However toxic effects soon became apparent as convulsions and arrythmias in patients, and addiction amongst medical staff were reported. The search for an alternative agent resulted in the discovery of other esters, and later amides. All were less toxic then cocaine but had differing cardiac and neurotoxic effects. Of particular note was the development of the amide bupivacaine that has a longer duration of action than lignocaine but is less toxic then cocaine. In the 1960s bupivacaine rapidly became globally popular especially for epidural pain relief in labour. In 1979 Albright reported six cases of cardiovascular collapse after presumed intravascular injection of bupivacaine or etidocaine (related to lignocaine). One caudal injection resulted in the death of a pregnant woman. In 1984, further reports of the toxic effects of bupivacaine were published by Plumer who collected 35 incidents involving intravenous injection of bupivacaine in pregnant women, ofwhomonly seven survived***(Plumer., 1984).***

Later, in 1991, Chadwick et al. presented data from the North American closed claims study, which reported between 1975 and 1985. He listed 12 maternal deaths after regional anaesthesia, and 19 incidences of convulsions, of which 18 occurred in patients with epidural anaesthesia, and 17 were thought to be due to local anaesthetic toxicity.

Outcomeswere poor with 83% of convulsions resulting in neurological injury or death to the mother, fetus, or both. In the UK, the complications seen with epidural anaesthesia in North America did not occur. This may have been due to the common UK practice of fractionating the administered dose. However in 1982, Heath5 reported five deaths (including two children) during intravenous regional anaesthesia (IVRA) with bupivacaine by non-anaesthetists. Following these reports, the use of bupivacaine for IVRA was prohibited and bupivacaine 0.75% solution was barred from obstetric use***(Chadwick et al., 1991).***

Bupivacaine HCL (1-butyl-2', 6' pipecoloxylidide hydrochloride)* is a long acting amide local anesthetic (Fig. 9). First synthesized in 1957 by Ekernstam at A. B. Bafors Laboratories in Molndel, Sweden, this drug has undergone trials and varying degrees of acceptance in virtually every area of local anesthetic practice***(Ekenstam et al., 1957).***

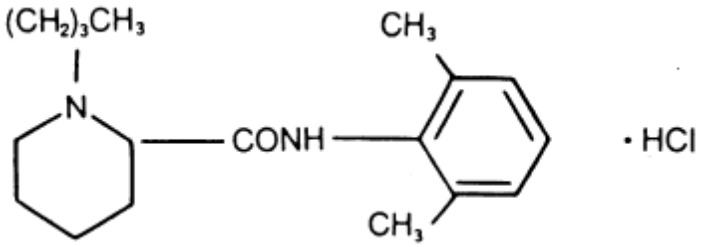


Fig. 9. *Chemical Structure of Bupivacaine*

Mechanism of Action

The mechanism ofaction ofbupivacaine is presumed to be the same as for other local anesthetics. Current local anesthetic theory holds that these compounds obstruct the inward flow of sodium ions through the nerve membrane, thus preventing the generation ofan action potential. Competitive binding to calcium sites is postulated to occur in the external

lipid layer of the nerve membrane with resultant secondary interference of mobile phosphate groups. Passage of sodium ions is blocked by preventing molecular membrane reconfiguration from the resting (sodium impermeable) to the active (sodium permeable) state. The increased duration of action of bupivacaine is ascribed to its affinity for nerve tissue***(Moore et al., 1960).***

Clinical Use

Bupivacaine is utilized for intraoperative local anesthesia, post operative analgesia and in the treatment of chronic pain. Bupivacaine is widely used in obstetrics. In lumbar epidural anesthesia the drug appears innocuous to mother and fetus. The acceptable therapeutic index is largely due to the small amount of drug needed per unit time. The indications for bupivacaine in obstetrical analgesia are enhanced by the insignificant motor blockade in concentrations less than 0.5%. Caudal blocks with bupivacaine for vaginal delivery are more efficacious due to the increased duration of analgesia, however fetal deaths have been reported secondary to paracervical block. This latter method of administration is contraindicated unless epidural block is incomplete or unavailable at a given institution. Excellent sensory anesthesia is reported with 0.5% bupivacaine epidural blocks for thoracic and abdominal surgery. The increased duration of action postpones the patients initial request for post operative analgesics. Continuous thoracic epidural infusion of 1.-0% bupivacaine does not provide analgesia of greater duration than lesser concentrations of bupivacaine***(Moir et al., 1976).***

Furthermore, tachyphalaxis, extensive segmental spread, urinary retention, high plasma drug concentrations, and inadequate operative anesthesia may occur. Intraoperative anesthesia by intercostal injection of

bupivacaine is effective, with a duration of four to five hours. Bupivacaine combined with 2-chlorprocaine for brachial plexus blocks provides rapid onset and an increased duration of anesthesia over 2-chlorprocaine alone. No toxic reactions and a quiescent post operative period are reported. ***(Galway et al., 1975).***

In ulnar nerve block, bupivacaine 0.25% or 0.5% provides excellent sensory and sympathetic anesthesia, but motor paralysis is not complete. Initial onset for sensory fibers in within eight minutes. For intravenous regional anesthesia, bupivacaine provides rapid onset (3-5 minutes), good muscle relaxation, and fewer toxic reactions relative to lidocaine. Bupivacaine has also been used in non-surgical procedures. Epidural administration has provided total resolution of non-malignant chronic pain. In a limited study, intra-gasserian ganglionic injection of bupivacaine moderated exacerbations of trigeminal neuralgia***(Adler., 1975).***

Clinical features of local anaesthetic toxicity

The clinical manifestations of toxicity are generally neurological, cardiac or both in origin. Howan individual presents with toxicity is variable as they may demonstrate either cardiac and neurological symptoms together, or symptoms solely from one system. ***(Chadwick et al., 1991).***

Neurological symptoms of toxicity

In the brain, local anaesthetics have a bi-phasic effect. Initially circulating molecules penetrate rapidly and block inhibitory interneurones resulting in excitatory phenomena such as a metallic taste, oral tingling, visual disturbances, ringing in the ears, tremors and dizziness, leading to

convulsions. In the second phase, all the neurones are blocked resulting in apnoea and coma***(Chadwick et al., 1991).***

Cardiac symptoms of toxicity

Cardiac symptoms occur as a result of blocking myocardial Na channels, slowing the cardiac action potential and so causing bradyarrhythmias such as heart block and asystole. Paradoxically, the persistent blockade of myocardial Na channels can also result in re-entrant arrhythmias and ventricular tachycardia and fibrillation. Local anaesthetics also have a direct depressant effect reducing the contractility of the myocardium. Bupivacaine should be speciallynoted here as it binds rapidly to myocardial Na channels and so can quickly produce toxic sequelae. However, due to high protein binding, it stays avidly bound and so produces prolonged effects***(Heath., 1982).***

Treating local anaesthetic toxicity

This should be supportive, treating convulsions with antiepileptics, and managing cardiac arrhythmias according to established guidelines. However, it is well recognized that the cardiac complications are resistant to treatment and require prolonged cardiopulmonary resuscitation (CPR) reputedly with limited success. Cardiopulmonary bypass was possibly the only effective method of treatment. It is important to note however, that the reputation for poor outcome in pregnant women may in part be due to the poor survival from Plumer's series who were resuscitated before the importance of caval compression was understood***(Plumer., 1984).***

The last 10 years has seen the emergence of a new treatment for local anaesthetic toxicity. After a patient deficient in carnitine, essential for the intracellular transport of fatty acids, the main myocardial energy

substrate, demonstrated an increased sensitivity to bupivacaine-induced cardiac dysrrhythmias, investigators considered whether intracellular lipid affected sensitivity to local anaesthetic toxicity. It had previously been established that ischaemic myocardial cells accumulated intracellular fatty acids. It was therefore proposed that an increased level of lipid rendered ischaemic cells more susceptible to arrhythmias. By infusing lipid it was hypothesized that an increased sensitivity to bupivacaine toxicity would be observed***(Weinberg et al., 1998)***.

In fact the opposite was shown. Infusing lipid into rats rendered them more resistant to bupivacaine-induced asystole. This effect was confirmed in anaesthetised rats which were pre-treated and resuscitated from bupivacaine induced asystole with lipid infusions. A subsequent study treating dogs with bupivacaine-induced cardiac toxicity showed that lipid infusion successfully resuscitated all subjects whether given immediately or after several minutes of CPR.***(Weinberg et al., 2003).***

Given that there was no effective and widely available treatment for local anaesthetic toxicity, and clinical trials would be impossible to carry out, the authors of the original studies offered lipid infusion therapy as a possible treatment in refractory arrests. They set up a website (www.lipidrescue.org) to promote its use and provide a forumto present reports of its use in humans as part of resuscitative measures in local anaesthetic toxicity. To date there are 11 such case reports of successful resuscitation of local anaesthetic toxicity, both cardiac and neurological sequelae, using lipid infusions. The exact mechanism for its action is unclear. One theory is that the lipid emulsion acts as a ‘lipid sink’ in the plasma compartment, capturing the local anaesthetic molecules and

making them unavailable to the tissue. Indeed this premise is the basis for current research into its application in other overdose/poisoning scenarios with lipophilic drugs. If this simple theory held true, one would expect that plasma concentrations of local anaesthetic agent would increase after lipid administration. However a recent case report of its successful use in local anaesthetic toxicity demonstrated that plasma concentrations actually decreased and more rapidly then would be explained by pharmacokinetic principles***(Litz et al., 2008).***

This would suggest that the mechanism may be one of increasing metabolism and distribution of the local anaesthetic. Another theory suggests that as bupivacaine can inhibit fatty acid utilisation by cardiac mitochondria, lipid could act to counter this effect. As a result of the evidence and successful case reports, the use of lipid infusions has been recommended by the Association of Anaesthetists of Great Britain and Ireland (AAGBI) in its guidelines for treating local anaesthetic toxicity a summary of which is presented in Tab. 1.

Tab.1 *.AAGBI Guidelines for the treatment of local anaesthetic toxicity*.
(The association of anaesthetists of Great Britain and Ireland; 2007).

1. Recognize the patient is exhibiting signs of local anaesthetic toxicity
2. Stop injecting the local anaesthetic
3. CALL FOR HELP and reassure the patient as best you can
4. Give 100% O2 and maintain the airway, if necessary, by performing a rapid sequence induction with cricoid pressure and secure airway with an endotracheal tube
5. Manage seizures and arrythmias but recognize they may be refractory to treatment
6. Continually assess cardiovascular status throughout and institute prompt cardiopulmonary resuscitation if arrest occurs consider cardiopulmonary bypass if available consider lipid infusion
7. If treating with lipid infusion #give initial bolus of 1.5ml.kg-1 of Intralipid 20% #continue CPR #start infusion at 0.25ml.kg-1.min-1 #give two further boluses at 5 minute intervals #after a further 5 minutes, increase rate to 0.5ml.kg-1.min-1

Clonidine

DEFINITION

Clonidine is primarily an α2 agonist used primarily for its antihypertensive effects (α2 to α1 receptor ratio of 200:1). Alpha-2 receptors are adrenoreceptors that are located primarily on presynaptic nerve terminals. Activation of these receptors inhibits adenylate cyclase activity, which in turn decreases the entry of calcium into the neuronal terminal, which limits norepinephrine release. This leads to an overall decrease in sympathetic outflow, causing peripheral vasodilatation, as well as negative chronotropic effects, therefore causing a reduction in blood pressure. This decrease in central sympathetic outflow does not affect baroreceptor reflexes, therefore not causing orthostatic hypotension. Stimulation of these receptors in the central nervous system has also been shown to have sedative properties***(Moss and Renz., 2005).***

HISTORY

Clonidine was synthesized in the early 1960s, and found to produce vasoconstriction that was later shown to be mediated by postsynaptic a2-adrenergic receptors in blood vessels ***(Hoffman and Lefkowitz.,1996).***

During clinical trials of clonidine as a topical nasal decongestant, the drug was found to cause hypotension and sedation. Paediatricians have extensively employed the drug in children for more than 20 years in diagnostic and therapeutic approaches. The first report concerning the use of clonidine in children was published in 1973: therapeutic approach to migraine with clonidine was documented. The second article published (in 1975) was an anecdotal report of accidental clonidine poisoning. Oral clonidine was shown to stimulate GH release in the middle of the 1970s ***(Lal et al., 1975).***

And in 1979 was successfully applied as a test for GH deficiency in children with short stature. For a period of time, a growing body of literature on this reliable test was available. Treatment of hypertension with clonidine was started in children in the same year. Thereafter, clonidine reportedly had therapeutic value in the treatment of Tourette syndrome which is a neuropsychiatric disorder characterized by changing motor and phonictics, compulsive actions, and other behavioural symptoms. Paediatricians and child psychiatrists also confirmed successful treatment with clonidine for children with attention-deficit hyperactivity disorder (ADHD) ***(Siegel and Lee., 1992).***

Since the early 1980s, clonidine small amounts of clonidine (10 µg·kg-1) induced suppression test has been used to differentiate essential hypertension from phaeochromocytoma as an adjunct to other diagnostic tests. Currently, clonidine is commonly prescribed for children with hypertension (second-line drug), Tourette syndrome, or ADHD in doses of 3–10 µg·kg-1 ***(Gelman et al., 1996).***

PHARMACOLOGY

Clonidine is N-(2,6 dichlorophenyl)-4,5-dihydro-1H- imidazol-2-amine (Fig 10) with a formula of C9H9Cl2N3.

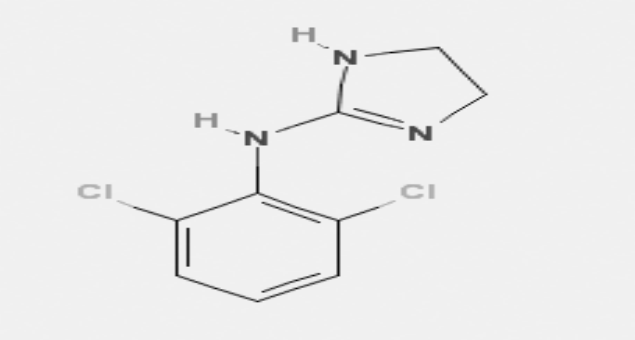


Fig. 10 chemical formula of Clonidine(C9H9Cl2N3)

Catecholamine receptors are classically divided into two main categories, α and β adrenoceptors. α -adrenoceptors are classified into subtypes 1A, 1B, 1D, 2A, 2B, and 2C, and β adrenoceptors into subtypes 1–3 and, in generally, guanine nucleotide-binding regulatory proteins (G proteins) mediate their actions. α2-Adrenoceptors decrease intracellular adenylcyclase activity through G_i or directly modify the activity of ion channels such as the Na^+/H^+ antiport, Ca^{2+} channels, or K^+ channels while β -adrenoceptors increase adenylcyclase activity through Gs. Finally, α 1- adrenoceptors are coupled to phospholipase C through G_q or directly to Ca^{2+} influx. Adrenoceptors located on the noradrenergic neurons are considered autoreceptors. In general, noradrenergic autoreceptors located in the somatodendritic area inhibit impulse discharge of neurons and those on noradrenergic axon terminals inhibit the release of norepinephrine. Adrenoceptors located on non-noradrenergic neurons are considered heteroreceptors. In intact animals, subtype α_{2C} is the most common (80%) followed by α_{2A} (20%), while α_{2B} is rare in the dorsal root ganglion***(Cooper et al., 2006).***

MECHANISM OF ACTION

Alpha-2 adrenergic agonists produce clinical effects by binding to alpha-2 receptors of which there are 3 subtypes: alpha-2a, alpha-2b and alpha-2c. Alpha- 2a receptors mediate sedation, analgesia and sympatholysis. Alpha-2b receptors mediate vasoconstriction and possibly anti-shivering mechanisms. The startle response reflects activation of alpha-2c receptors and it is the response of mind and body to a sudden unexpected stimulus, such as a flash of light, a loud noise (acoustic startle reflex), or a quick movement near the face. In human beings, the reaction includes physical movement away from the stimulus, a contraction of the muscles of the

arms and legs, blinking and it also includes blood pressure, respiration, and breathing changes. Clonidine is a centrally acting selective partial adrenergic agonist (alpha-2: alpha-1=220:1). Alpha-2 receptors are found densely in the pontine locus coeruleus which is an important source of sympathetic nervous system innervation of the forebrain and a vital modulator of vigilance. The sedative effects evoked by alpha-2 agonists most likely reflect inhibition of this nucleus.

Clonidine also stimulates alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre. As a result, there is a decrease in the sympathetic nervous system outflow from the central nervous system (CNS) to the peripheral tissues. This causes central and peripheral attenuation of sympathetic outflow and central activation of nonadrenergic imidazoline preferring receptors. Decreased sympathetic nervous system activity is manifested as peripheral vasodilatation and a decrease in systolic blood pressure, heart rate and cardiac output***(De Vos et al., 1994).***

The ability of clonidine to modify the potassium channels in the CNS and thereby hyperpolarize the cell membranes may be the mechanism for profound decrease in anaesthetic requirements produced by clonidine. Neuraxial placement of clonidine inhibits spinal substance P release and nociceptive neuron firing produced by the noxious stimulation. Alpha-2 afferent terminals are situated centrally and peripherally, in the superficial laminae of the spinal cord and several brain stem nuclei. This suggests that clonidine's analgesic effects are more pronounced after neuraxial administration. Clonidine synchronously decreases the cold-response threshold while slightly increasing the sweating threshold thus suggesting that it acts on the central thermoregulatory system rather than preventing shivering peripherally***(De Witte J, Sessler.,2002).***

PHARMACOKINETICS

Clonidine is rapidly absorbed after oral administration. It reaches a peak plasma concentration within 60-90 minutes. The bioavailability of the drug is about 75-95%. About 20-40% of the drug is bound to protein. 50% of the drug is metabolized in the liver to inactive metabolites which are excreted in the urine and the half life is about 12-33 hours. As clonidine is lipid soluble, it penetrates the blood-brain barrier to reach the hypothalamus and medulla. It does not require transformation into another substance prior to its action2 . Clearance of clonidine in neonates is about onethird of that described in adults due to immature elimination pathways and it reaches about 82% of adult rate by one year of age. Hence maintenance dosing which is a function of clearance should be decreased in neonates and infants when using a target concentration approach. Rectal administration of 2.5 mcg.kg-1 of clonidine in children, approximately 20 minutes before induction of anaesthesia, achieves a plasma concentration within the range known to be clinically effective in adults***(Potts et al., 2007).***

PHARMACODYNAMICS

Haemodynamic effects of clonidine in children

During isoflurane anaesthesia in children aged 1—10 years, we have documented a significant reduction in mean arterial blood pressure (MABP) (26.3%, SD 13.6) after intravenous clonidine 2.5 mg/kg. A minor and brief reduction in heart rate was also observed despite rectal premedication with atropine 40 mg/kg and, thus, pretreatment with an anticholinergic is recommended when clonidine is used. Increased post-operative blood pressure stability is observed when a continuous post-

operative epidural infusion of clonidine is used in children ***(Bergendahl et al., 2002).***

Peri-operative sedation, axiolysis and analgesia In their initial study, Mikawa et al. reported that oral clonidine 4 mg/kg administered 105 min prior to anaesthetic induction provided improved sedation, better quality of separation from parents, and a higher acceptance rate of mask application compared with clonidine 2 mg/kg or diazepam 0.4 mg/kg. These beneficial effects of clonidine premedication were later supported by Ramesh and colleagues who showed that oral clonidine 3 mg/kg produced comparable sedation to diazepam 0.2 mg/kg, but was also able to attenuate the haemodynamic response to endotracheal intubation without any prolongation of the recovery time from anaesthesia ***(Ramesh et al., 1997).***

In neither of these studies were any adverse effects, such as bradycardia, hypotension or respiratory depression, noted. In paediatric surgical patients, the sedative and anxiolytic effect of oral clonidine (4-5 mg/kg) has been found to produce similar degrees of sedation and anxiolysis as oral midazolam (0.1- 0.5 mg/kg). As demonstrated by Sumiya in 2003, plasma clonidine concentrations of 0.3—0.8 ng/ml produce satisfactory sedation without changes in haemodynamic parameters***(Sumiya et al., 2003).***

Mikawa et al. suggests that oral clonidine premedication (4 mg/kg) facilitates post-operative analgesia in children undergoing minor surgery. In children undergoing ophthalmological surgery, the same group has also shown that oral clonidine premedication augmented post-operative pain relief using a diclofenac suppository or intravenous flurbiprofen. Despite these data showing an analgesic potential of clonidine in children, contradictory data with regards to analgesia has been reported when clonidine is used in the context of adeno-tonsillectomy. In this

subgroup of paediatric patients, Reimer et al. found that oral premedication with clonidine (4 mg/kg) resulted in similar analgesia as compared with intravenous fentanyl (3 mg/kg) ***(Nishina et al., 2000)***, whereas results from a similar study by Fazi et al. (clonidine 4 mg/kg as oral premedication) showed an increased post-operative demand for analgesia when compared with children treated with oral midazolam (0.5 mg/kg). Local infiltration of ropivacaine combined with clonidine in the tonsillar fossae prior to tonsillectomy has recently been reported to produce long-lasting improvement of post-operative pain in paediatric patients. In a recent study, we have shown that rectal premedication with clonidine 5 mg/kg is associated with a significant reduction in pain scores during the early post-operative period after adeno-tonsillectomy when compared with midazolam 300 mg/kg.

The use of clonidine was also associated with slightly increased sedation ratings during the first 24 postoperative hours. However, this sedative effect is in agreement with an unequivocal parental preference of a calm and sedated child during the early postoperative period ***(Giannoni et al., 2001).***

Effects on shivering, post-operative nausea and vomiting and post-operative agitation-confusion

Both oral and caudal clonidine has been reported to reduce the incidence of post-operative vomiting in children. After paediatric strabismus surgery, Handa et al. have shown that pretreatment with oral clonidine 4 mg/kg enhances the antiemetic effect of propofol when compared with midazolam 0.4 mg/kg , but Gulhas et al. could not corroborate these results in a similar study comparing oral clonidine 4 mg/kg with placebo ***(Gulhas et al., 2003).***

In adults, clonidine decreases the incidence of post-operative shivering and is an effective alternative in the treatment of already established shivering. In our recent publication, we reported a possible preventive action of clonidine on post-operative shivering as none of the patients in the clonidine group shivered whereas 11% of patients in the midazolam group were found to shiver during the recovery room stay. For treatment of shivering, adult data indicates that less than two patients need to receive clonidine 1.5 mg/kg for one to stop shivering in 5 min after drug administration ***(Kranke et al., 2003).***

The use of sevoflurane in children, especially in preschool boys, has been associated with an increased incidence of early post-operative confusion and delirium. After both caudal and intravenous administration of clonidine in children, Bock et al. have demonstrated a dose-dependent prevention of agitation after sevoflurane anaesthesia. In keeping with the results presented by Kulka et al., we recently showed that clonidine reduces the incidence of post-operative confusion in the children less than 5 years of age compared with midazolam ***(Kulka et al., 2001).***

Effects on the stress response secondary to endotracheal intubation and surgery

In line with previous adult findings, several paediatric studies have shown that oral administration of clonidine is capable of blunting both the catecholamine release and the haemodynamic response secondary to endotracheal intubation in otherwise

healthy children 7—17 years. However, as the adrenergic stress response to routine tracheal intubation in children 1—9 year is short lived and of limited magnitude, as indicated by the lack of neuropeptide Y release ***(Bergendahl et al.,1999)***, routine attempts to attenuate the stress response after tracheal intubation in otherwise healthy children might be debatable.

In a recent study by Nishina et al., oral clonidine premedication was found to attenuate the hyperglycaemic response to surgical stress. These authors suggested that a 2% glucose infusion would to be optimal in order to maintain blood glucose concentrations within the physiologic range when using this approach***(Nishina et al., 1998).***

Anaesthetic sparing effect

Oral clonidine premedication (2—4 mg/kg) in children aged 7—12 years successfully decreases the dose of intravenous barbiturate required for induction of anesthesia. Compared with placebo, oral clonidine treatment with 4 mg/kg in children undergoing minor surgery has been demonstrated to both reduce the halothane requirements for maintenance of anaesthesia as well as the MACTI of sevoflurane for endotracheal intubation ***(Nishina et al., 1997).***

Supplement to regional anaesthesia and post-operative analgesia

After caudal blockade in children, the administration of clonidine (1—5 mg/kg) as an adjunct to local anaesthetics has repeatedly been found to prolong and improve post-operative pain relief. The addition of clonidine (> 0.1 mg/kg/h) to a continuous epidural infusion of ropivacaine has also been found to improve the quality of post-operative pain relief in children. Kaabachi in 2002 and Rochette et al. in 2004 have suggested that intrathecal clonidine 2 mg/kg in a combination with bupivacaine is associated with extending the duration of postoperative analgesia with moderate side-effects ***(Rochette et al.,2004).***

Oral administration has been shown to be less potent than epidural clonidine regarding the enhancement of epidural blockade in adults. However, the administration of oral clonidine 5 mg/kg has been reported to cause an increased duration of bupivacaine-induced caudal anesthesia in children. Furthermore, in a recent study, Hansen et al. have

demonstrated that the analgesic effect of clonidine 2 mg/kg as an adjunct to caudal block with bupivacaine 0.25%, 0.5 ml/kg is similar whether administered intravenously or caudally. The popularity of the use of adjunct clonidine has recently been illustrated by a survey of regional paediatric anaesthesia from the UK where 26% of respondents used clonidine as adjuvants to local anaesthetics for caudal blockade. Two recent reviews have also been published regarding the use of adjuvants to local anaesthetics in children ***(Ansermino et al.,2003).***

TOXICOLOGY AND SIDE-EFFECTS

Administration of clonidine may be accompanied by drowsiness, dry mouth, bradycardia, orthostatic hypotension and impotence. Abrupt withdrawal of the drug could lead to rebound hypertension resulting in a hypertensive crisis. Hence clonidine should be continued throughout the perioperative period. Clonidine may increase blood glucose concentration by inhibiting insulin release.

Caudal clonidine has a large margin of safety in healthy children as reported in three cases where 100 times the dose for a single shot caudal was given. Apart from excessive somnolence for a day, these children had no respiratory depression or haemodynamic instability***(Meyer and Cambray., 2008).***

A five year old child with cerebral palsy and seizure disorder was given clonidine in excessive doses by the mother to control restlessness. The child had bradycardia and hypotension after induction and required resuscitation92. In a multicentre study conducted by Spiller et al children younger than twelve years of age who reported to six poison centers with clonidine ingestion were followed for a minimum of 24 hours***(Goldfinger and Tripi., 2007).***

Though clinical effects were common, severe adverse effects occurred only in 10% of the patients. The dose ingested was reported for 90 patients (80%). 61 (68%) children ingested 0.3 mg and none had coma, respiratory depression, or hypotension. The lowest dose ingested that resulted in coma and respiratory depression was 0.3 mg (0.015mcg/kg). The authors have recommended a direct medical evaluation for :

(1) all children 4 years of age and younger with unintentional clonidine ingestion of 0.1 mg .

(2) ingestion of 0.2 mg in children 5 to 8 years of age .

(3) ingestion of 0.4 mg in children older than 8 years of age.

Observation for 4 hours may be sufficient to detect patients who will develop severe effects***(Spiller et al., 2005).***

Sinha et al reviewed cases of clonidine poisoning presenting to Royal Children's Hospital, Melbourne, Australia over the period from 1997 to 2001. Twentyfour cases of clonidine poisoning were identified over the 5 year period. Nine patients ingested their own medication, which was prescribed for attention-deficit hyperactivity disorder. Clonidine was prescribed for children in 16 cases (67%) for other purposes. Impaired conscious state and bradycardia were the most common presenting features. Activated charcoal was given in 14 cases and volume expansion in six. There were 12 children (50%) who required admission to the intensive care for monitoring, including three who received mechanical ventilation. The average length of stay was 25.7 hours with no long-term complications***(Sinha and Cranswick., 2004).***

Antagonist:

The adverse clinical effects of clonidine and dexmedetomidine can be readily reversed with the specific antagonist **atipamezole** ***(Scheinin et al.,1998).***

Dexmedetomidine

DEFINITION:

Dexmedetomidine is a highly specific and selective alpha-2-adrenergic agonist with sedative, anxiolytic, and analgesic effects . The sedative state produced by dexmedetomidine is unique in a number of ways and is dose dependent . At low doses, it produces sedation wherein the patient is drowsy but remains arousable and cooperative. When the dose is large enough, it produces deep sedation or even general anesthesia. Minimal respiratory depression is observed even when large doses are used .

The sedative effect mimics natural stage 2 nonrapid eye movement sleep, which is evident from the electroencephalograph . Because it has minimal respiratory depressant effect and only modest cardiovascular effects in the majority of patients, the safety margin of this drug is favorable compared to gamma-aminobutyric acid receptor agonists such as propofol and benzodiazepines. Recently, dexmedetomidine has been investigated extensively in the pediatric population and there is now increasing evidence to support the use of this drug as sedative and anesthetic adjunct in children. The perioperative application of dexmedetomidine in children is discussed. However, although we have good clinical data in children, it is currently only approved by the US FDA for continuous infusion of up to 24 h in the adult intensive care unit. Hence, the uses of dexmedetomidine in children described in this review are 'off-label'***(Huupponen et al., 2008)***

HISTORY

The first α-2 adrenoceptor agonist was synthesized in the early 1960s to be used as a nasal decongestant. Early application of the new substance, now known as clonidine, showed unexpected side effects, with sedation for 24 hours and symptoms of severe cardiovascular depression. Subsequent testing led to the introduction of clonidine as an antihypertensive drug in 1966. Over the years, clonidine gained acceptance as a powerful therapy not only for high blood pressure but also for the management of alcohol and drug withdrawal, for adjunctive medication in myocardial ischemia, and for pain and intrathecal anesthesia. The use of α-2 adrenoceptor agonists as anesthetics is not new. Veterinarians employed xylazine and detomidine for a long time to induce analgesia and sedation in animals , and much of current knowledge was gained from this application. It has recently become evident that complete anesthesia is possible by employing new, more potent α-2 agonists, such as medetomidine and its stereoisomer, dexmedetomidine**(*Gertler et al., 2001*)**.

Dexmedetomidine (Precedex®; Abbott Labs, Abbott Park IL) was approved in the United States, by the Food and Drug Administration (FDA), at the end of 1999, for use in humans as a short-term medication (< 24 hours) for sedation/analgesia in the intensive care unit (ICU) and, thereafter, in some other countries (Czech Republic, for example). Its unique properties render it suitable for sedation and analgesia during the whole perioperative period. Its applications as a premedication, as an anesthetic adjunct for general and regional anesthesia, and as a postoperative sedative and analgesic are similar to those of the

benzodiazepines, but a closer look reveals that the α-2 adrenoceptor agonist has more beneficial side effects**(*Gertler et al., 2001*)**.

PHARMACOLOGY

Dexmedetomidine is chemically described as (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1 H-imidazole monohydrochloride. It has a molecular weight of 236.7. It has a pH in the range of 4.5-7. It is water soluble, has a pKa of 7.1. Its partition coefficient in octanol: water at pH 7.4 is 2.89 (Figure 11).

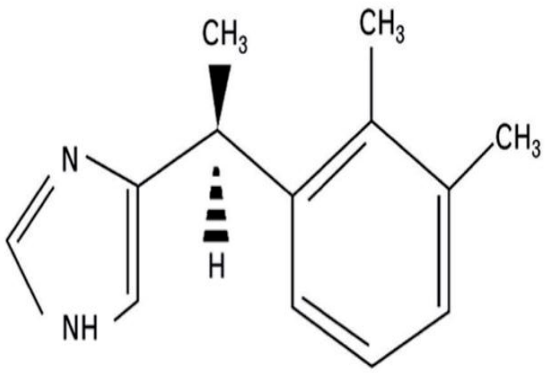


Fig. 11:Chemical structure of dexmedetomidine
(Chrysostomou and Schmitt., 2008)

Dexmedetomidine is the pharmacologically active dextro enantiomer of medetomidine, the methylated derivative of etomidine. It is considered primarily as α-2 adrenoceptor agonist, but also incorporates an imidazoline structure, thus having an agonist effect on imidazoline receptors.

Dexmedetomidine is chemically related to clonidine, but is approximately eight times more specific for α-2 adrenoceptors with α-2: α-1 selectivity ratio of 1620:1, compared with 200:1 for clonidine, especially for the 2a subtype, which makes dexmedetomidine more effective than clonidine for sedation and analgesia. Its effects are dose-dependently reversed by

administration of a selective α-2 antagonist, such as **atipamezole*(Panzer et al.,2009).***

MECHANISM OF ACTION

The hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons in the locus ceruleus of the brain stem (a small bilateral nucleus that contains many adrenergic receptors), which is the primary site in modulating wakefulness. When the α-2 adrenergic receptor is activated, it inhibits adenylyl cyclase. This latter enzyme catalyzes the formation of cyclic AMP (cAMP), a crucial second messenger molecule that acts in many catabolic cell processes.

By reducing the amount of cAMP in the cell, dexmedetomidine favors anabolic over catabolic pathways. Simultaneously, there is an efflux of potassium through calcium-activated potassium channels and an inhibition of calcium entry into calcium channels in nerve terminals.

(Khan et al., 1999).

The change in membrane ion conductance leads to a hyperpolarization of the membrane, which suppresses neuronal firing in the locus ceruleus as well as activity in the ascending noradrenergic pathway. The locus ceruleus is also the site of origin for the descending medullospinal adrenergic pathway, which is known to be a key mechanism in regulating nociceptive neurotransmission. The similar mechanisms of α-2 receptors and opioid receptors in this area of the brain have contributed to the thought that there must also be extra-spinal sites of action. When these sites are stimulated, they decrease the firing of nociceptor neurons stimulated by peripheral A and C fibers and also inhibit the release of

their neurotransmitters. The analgesic effects are believed to be in the dorsal horn of the spinal cord ***(Kamibayashi and Maze., 2000)***.

When a hypnotic dose of dexmedetomidine was administered to laboratory animals, norepinephrine release from the locus ceruleus was inhibited. The absence of inhibitory control over the ventrolateral preoptic nucleus (VLPO) resulted in the release of -aminobutyric acid (GABA) and galanin, which further inhibited the locus ceruleus and tuberomamillary nucleus (TMN). This inhibitory response also causes a decrease in the release of histamine, which results in a hypnotic response. This response is similar to that found in normal sleep in that the reduction of norepinephrine release by the locus ceruleus triggers the release of GABA and galanin by the VLPO. These neurotransmitters further inhibit norepinephrine release by the locus ceruleus and suppress histamine secretion by the TMN. The reduced occupancy of the histamine receptors on the cells of the subcortical areas induces a hypnotic state ***(Nelson et al., 2001)***.

PHARMACOKINETICS

Dexmedetomidine follows linear or zero-order kinetics, meaning that a constant amount of the drug is eliminated per hour rather than a constant fraction of the drug eliminated per hour, which is characteristic of first order kinetics. After intravenous administration (IV) in healthy adult volunteers, dexmedetomidine has an onset of action after approximately 15 minutes. Peak concentrations are usually achieved within 1 hour after continuous IV perfusion. Dexmedetomidine is also absorbed systemically through the transdermal, oral, or intramuscular routes, with a mean bioavailability from the latter two routes of 82 and 104%, respectively.

(Panzer et al.,2009).

Protein binding to serum albumin and α1-glycoprotein is reported to be approximately 94% and remains constant despite varied concentrations of the drug. The bound fraction is decreased significantly in patients with hepatic dysfunction, compared with healthy patients; therefore, a dose reduction in patients with hepatic dysfunction may be required.
It has a rapid distribution phase. Its steady state volume of distribution is 118 L and its distribution half-life (t ½ α) is 6 min in adults over the manufacturer-suggested dose ranges of 0.2-0.7 μg.kg-1.h-1, an elimination half-life (t ½ β) of between 2.0 and 2.5 hours and a clearance of 39 L.h-1***(Dyck and Shafer.,1993).***

Total plasma clearance of dexmedetomidine is age independent; thus, similar rates of infusion can be used in childrenand adults to effect a steady state plasma concentration. However, in patients aged ≥ 65 years, a greater incidence of hypotension and bradycardia was reported; therefore, a dose reduction in this population may be warranted.

(Chrysostomou and Schmitt., 2008).

In children younger than 2 years of age, the volume of distribution at steady state is increased, suggesting that higher doses are required to achieve steady state; but t ½ β is prolonged, which may result in increased drug accumulation with time ***(Vilo et al., 2008)***.

Dexmedetomidine is extensively metabolized in the liver through glucuronide conjugation and biotransformation by the cytochrome P450 enzyme system. There are no known active or toxic metabolites. However, hepatic clearance may be decreased by as much as 50% of normal with severe liver disease. No differences have been seen between

healthy patients and those with renal impairment. The metabolites are eliminated to the extent of 95% in the urine and 4% in the feces. Considering that the majority of the metabolites are excreted in the urine, there is a theoretical risk that accumulation may result with prolonged administration ***(De Wolf et al., 2001)***.

PHARMACODYNAMICS

Central Nervous System

Sedation is one of the most important effects of α2-adrenergic drugs. This was an adverse effect observed in hypertensive patients treated with clonidine. However, it has been observed that such side-effect was beneficial during anesthesia because it decreased the need for anesthetic drugs and started to be used as preanesthetic medication ***(Hayashi Y, Maze., 1993).***

Sedation and hypnosis are dose-dependent and sedation has a fast onset (approximately 30 minutes) depending on the drug. α2-adrenergic receptors activation in the CNS, with decreased norepinephrine levels, is believed to be the cause of sedative-hypnotic effects of those receptors' agonists.

Liu et al. ***(Liu et al., 1993)*** have shown recovery of epidural clonidine with a specific α2-adrenergic receptor antagonist, namely iombine. α2-agonists sedative effects are significantly potentiated when associated to benzodiazepinics. *Locus coeruleus* has been recently identified as the region responsible for sedation ***(Dyck and Maze., 1993)***.

Major ascending and descending noradrenergic ways are originated in this important area. The activation of α2-adrenergic receptors in this area suppresses its activity resulting in a major increase in inhibitory

interneurons activity, such as those part of the γ-aminobutyric acid (GABA) pathway, determining CNS suppression. Another important α2-agonists characteristic is the anxiolytic effect, comparable to benzodiazepinics drugs ***(Gertler et al., 2001)***.

However, high α2-agonist doses may lead to anxiogenic effects due to the non-selective activation of α1-adrenergic receptors. α2-adrenergic receptors activation produces intense analgesic response by involving supra-medullary, and especially medullary receptors, including post-synaptic α2 receptors of noradrenergic descending pathways, of cholinergic neurons and of nitric oxide and encephalines release. Dexmedetomidine has an important pain modulating role for inhibiting nervous conduction through A_and C fibers. Different classes of drugs, such as α2-agonists and opioids, are clearly synergistic, thus decreasing the need for each component, which in practice is of great value since it decreases adverse effects of each drug. To show that α2-agonists and opioids induce analgesia by different mechanisms, naloxone was experimentally used in patients who had received dexmedetomidine and the analgesic effect was not reverted by the opioid antagonist ***(Jalonen et al., 1997)***.

For acting in the CNS, α2-agonists are able to dramatically decrease the need for other anesthetic drugs, however with a ceiling effect. This is because some drugs, depending on their α2-receptors selectivity, have partial agonist properties and activate α1 receptors, which could antagonize α2 agonist effects in the CNS. A major α2-agonist property is the ability to decrease halogenate requirements during anesthesia. With the advent of super-selective α2-agonists, such as dexmedetomidine, minimum alveolar concentration (MAC) is decreased up to 95% when

halothane is the halogenate of choice. However, MAC decrease outcomes are widely variable, with MAC decreasevalues of 50% to 90% with isoflurane and only 17% with sevoflurane, both associated to dexmedetomidine. In spite of its convulsant potential, there are no reports to date on dexmedetomidine-induced seizures***(Aantaa et al., 1997)***.

Cardiovascular System

α2-adrenergic agonists action on the cardiovascular system is divided in peripheral and central. The activation of pre-synaptic α2-adrenergic receptors on peripheral nerve terminations inhibits norepinephrine exocytosis, which partially explains arterial hypotension and bradycardia caused by the activation of such receptors. The incidence of arterial hypotension, with decreases above 20% of baseline values, may reach 30% ***(Gertler et al., 2001)***.

When the muscular route is used for preanesthetic medication, doses around 1 μg.kg-1 may cause important arterial hypotension with systolic blood pressure reaching 65mmHg and marked bradycardia, up to 30 beats per minute. Bradycardia may be prophylactically treated with atropine, however, the activation of post-synaptic α2-receptors causes vasoconstriction by acting on smooth arterial and venous muscles.

(Ruffolo., 2005).

The activation of vasomotor center α2 receptors in the CNS decreases sympathetic efflux with progressive circulating catecholamine decrease, thus potentiating parasympathetic nervous activity and leading to blood pressure decrease. Some CNS sites are very important in the activation of α2-agonist receptors, such as the solitary tract and, to a lesser extent, *locus coeruleus*, dorsal motor nucleus of vagus and lateral reticular nucleus ***(Kubo and Misu., 2001).***

α2-adrenergic receptors stimulation in the vascular endothelium leads to vasoconstriction and this is the explanation for transient arterial hypertension during intravenous dexmedetomidine infusion, thus opposed to the vasodilating action of the drug caused by central effects. This tensional lability is more often seen in the initial phase of continuous infusion when it is recommended a higher priming dose during a short period of time to reach the desired concentration in the effector site. Arterial hypotension is probably caused by a sympathicolytic action on the CNS and is mainly caused by the action of the drug on α2 post-synaptic receptors and on α1 receptors, although the high selectivity of the drug. As to coronary arteries circulation, there is a predominant vasodilating effect, probably by nitric oxide production in the coronary endothelium; however, a vasoconstrictor effect caused by small artery α2 receptors is also observed ***(Flack et al., 1987).***

Heart rate decrease is seen in variable degrees after dexmedetomidine administration. This may be explained by the activation of peripheral nerve termination pre-synaptic receptors activation, with decreased norepinephrine exocytosis and by asympathicolitic effect on the CNS. Imidazolinic receptors activation in the CNS also seems to contribute for α2-agonist-induced bradycardia ***(Alves et al., 2000).***

Somedrugs with agonist activity on imidazolinic receptors are being used as anti-hypertensive drugs. It is believed that such drugs acton CNS specific receptors and, moreover, have affinity with α2 receptors. Atrioventricular conduction changes with dexmedetomidine are not so marked as with clonidine, but they occur in a lesser degree. The drug of choice for handling bradyarrhythmias is atropine and some times high drug doses are needed to reach the desired effect.

Arterial hypotension is easily treated with vasoconstrictor drugs, such as ephedrine, which shows an increased vasomotor response in the presence of α2-agonist drugs. Metaraminol may not be indicated because the situation might be of associated arterial hypotension and bradycardia and metaraminol could further decrease heart rate***(Gertler et al., 2001)***.

Respiratory System

Although α2-agonists being able to cause hypoxemia, this has not been clinically observed in men. α2-agonists cause almost no respiratory depression as compared to opioids. Experimental studies have shown a 6%incidence of hypoxia in patients sedated with dexmedetomidine. Dexmedetomidine does not induce major respiratory depression, even when in high concentrations. In the postoperative period it may even improve respiratory depression caused by higher opioid doses. Dexmedetomidine as all α2-adrenergic agonists, does not potentiate opioid-induced respiratory depression ***(Hayashi and Maze., 1993).***

GI Tract

α2-adrenergic agonists have a marked anti-sialogogue effect which is useful in preanesthetic medication. However, a major dexmedetomidine effect is xerostomia (dry mouth), which is highly uncomfortable. In addition, there is an 11% incidence of nausea in patients sedated with dexmedetomidine ***(Dyck and Shafer., 2000).***

Endocrine System

In general, α2-agonist drugs directly inhibit insulin release by pancreatic _ cells, but they do not cause major hyperglycemia. In addition, for decreasing sympathetic stimulation, α2-adrenergic drugs, and especially

dexmedetomidine, markedly decrease surgical stress response, confirmed by the lower need for anesthetic agents when patients are sedated with dexmedetomidine ***(Dyck and Shafer., 2000).***

Renal System

α2-agonist drugs have induced diuresis in all animal studies and especially in men. This action varies according to the animal model. In men, α2-adrenergic agonists act by inhibiting antidiuretic hormone release, in addition to increasing glomerular filtration rate. Another mechanism of drugs such as dexmedetomidine is the inhibition of renin release together with the facilitation of atrial natriuretic peptide release***(Maze., 2002).***

TOXICOLOGY AND SIDE-EFFECTS

The teratogenic effects of dexmedetomidine have not been adequately studied at this time, but the drug does cross the placenta and should be used during pregnancy only if the benefits justify the risk to the fetus. No studies have been performed in children. As expected from the pharmacological profile, bradycardia and hypotension are the most common side-effects of dexmedetomidine. However, with the use of high concentrations there is also a potential for both pulmonary and systemic hypertension and direct or reflex bradycardia ***(Ebert and Maze., 2004).***

The incidence of postoperative bradycardia has been reported to be as high as 40% in healthy patients. These temporary effects have been managed with atropine, ephedrine, and volume infusion. Caution should be taken in those clinical situations where the sympatholytic actions of α-2 receptor agonists prove detrimental, such as in patients with left

ventricular dysfunction and when administered to patients who are volume depleted, vasoconstricted, or have severe heart block ***(Haselman., 2008).***

Recently, severe bradycardia leading to cardiac arrest has been reported with the use of dexmedetomidine. A closer look at these reports reveals several contributing factors that may have interacted, finally resulting in asystole. However, even if dexmedetomidine can probably not be held accountable as the only causative mechanism of these cardiac arrests, such case reports are important. They emphasize potentially deleterious effects that have significant implications for the safe use of these drugs in the critically ill, when multiple factors with negative chronotropic influences convene in a clinical setting, and underline the importance of adequate patient selection for the safe use of dexmedetomidine. In summary, the adverse effects of dexmedetomidine include initial hypertension, hypotension, nausea, bradycardia, atrial fibrillation, and hypoxia. Overdose may cause first degree or second-degree atrioventricular block. Most of the adverse events associated with dexmedetomidine use occur during or shortly after loading dose***(Ingersoll-Weng et al., 2004).***

Fentanyl

Fentanyl is a strong opioid agonist, a Schedule II substance, available in parenteral, transdermal, and transbuccal preparations. Fentanyl is the oldest synthetic piperidine opioid agonist, interacting primarily with mu `highly lipophilic and binds strongly to plasma proteins ***(Janicki and Parris, 2003)***.

Fentanyl was initially developed as a highly potent opioid analgesic to be used as the analgesic component of balanced anaesthesia. However, its high potency, unusual pharmacokinetics and physicochemical properties have widened the indications for the use of fentanyl significantly. While the initial usage was exclusively parenteral and the oral route is not an option due to a high first-pass effect, multiple new routes of administration have been studied. These findings have resulted in the development of a number of new preparations for indications ranging from longterm management of cancer and chronic pain through to on-demand treatment for postoperative and breakthrough pain***(Peng and Sandler, 1999).***

HISTORY

Fentanyl was first synthesized by Paul Janssen in 1960 following the medical inception of pethidine several years earlier. Janssen developed fentanyl by assaying analogues of the structurally related drug pethidine for opioid activity. The widespread use of fentanyl triggered the production of fentanyl citrate (the salt formed by combining fentanyl and citric acid in a 1:1 stoichiometry), which entered the clinical practice as a general anaesthetic under the trade name Sublimaze in the 1960s.

Following this, many other fentanyl analogues were developed and introduced into medical practice, including sufentanil, alfentanil, remifentanil, and lofentanil***(Stanley., 1992).***

In the mid-1990s, fentanyl was first introduced for widespread palliative use with the clinical introduction of the Duragesic patch, followed in the next decade by the introduction of the first quick-acting prescription formations of fentanyl for personal use, the Actiq lollipop and Fentora buccal tablets. Through the delivery method of transdermal patches, as of 2012 fentanyl was the most widely used synthetic opioid in clinical practice, with several new delivery methods currently in development, including a sublingual spray for cancer patients. Fentanyl and derivatives have been used as recreational drugs. Fatalities arising from its use have been recorded***(DailyMed. 2010).***

PHARMACOLOGY

Fentanyl [N-(1-phenethyl-4-piperidyl)propionanilide] is a synthetic, highly selective opioid agonist that works mainly at the m-opioid receptor, with some activity at the d and k receptors. Fentanyl is highly potent, being 100- to 300-fold more potent than morphine. Its high lipophilicity (octanol-water partition coefficient 816 vs 1.4 for morphine) allows rapid penetration into CNS structures. In addition to passive diffusion, active transport systems have been described for fentanyl uptake via the brain endothelium.

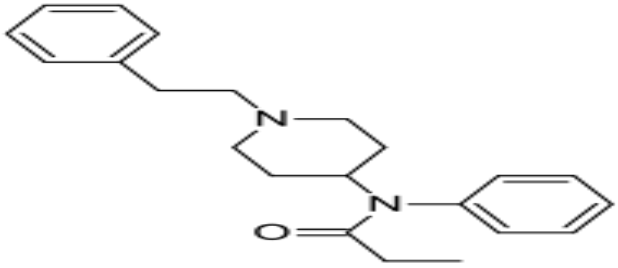


Figure 12 : *chemical formula of fentanyl{N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylpropanamide}*

(Henthorn et al., 1999).

Mechanisms of action

Fentanyl provides some of the effects typical of other opioids through its agonism of the opioid receptors. Its strong potency in relation to that of morphine is largely due to its high lipophilicity, per the Meyer-Overton correlation. Because of this, it can more easily penetrate the CNS. Fentanyl binds μ-opioid G-protein-coupled receptors, which inhibit pain neurotransmitter release by decreasing intracellular Ca2+ levels***(Stacey., 2006).***

PHARMACOKINETICS

Pharmacokinetic properties of fentanyl include a large volume of distribution (3.5–8L/kg, average 6 L/kg) and a high total body clearance (30–72 L/h). After an intravenous bolus, fentanyl is rapidly distributed from plasma into highly vascularized compartments before redistribution to muscle and fat tissue occurs. After an initial equilibration, fentanyl is released back into plasma from these storage sites, which accounts for its long elimination half-life of 3–8 hours***(Peng and Sandler, 1999).***

Thus, fentanyl has a short duration of action after a single bolus, but can accumulate after multiple boluses or continuous infusion. Fentanyl is primarily metabolized in the liver by cytochrome P450 (CYP) 3A4. The

main metabolite is norfentanyl; minor metabolites are hydroxypropionyl-fentanyl and hydroxypropionylnorfentanyl, which do not have relevant pharmacological activity. Approximately 75% of fentanyl is excreted via the kidney, with less than 10% as unchanged fentanyl. About 9% of metabolites are recovered in the faeces. In opioid-naive postoperative patients, fentanyl produces rapid and effective analgesia at minimum plasma concentrations between 0.6 and 1.5 ng/mL***(Mather., 1983).***

PHARMACODYNAMICS

The clinical effects of fentanyl, regardless of route of administration, are similar to those of other opioids, and are similarly dependent on both the dose and the degree of patient tolerance. At serum fentanyl concentrations of 0.63–1.5 ng/mL, postoperative analgesia is produced in most opioid-naive patients. Hypoventilation begins to manifest at concentrations >1.5 ng/mL, a subtherapeutic serum concentration for some***(Shibutani et al., 2005).***

With escalating doses, analgesia is preserved and mild sedation is noted. Patients in this state are easily arousable with physical stimulation. As concentrations increase further, deep sedation develops, requiring greater stimulation, and the arousal period shortens. Further increasing fentanyl concentrations produces coma, with the inability to arouse the patient. Respiratory depression essentially parallels sedation and analgesia, with the eventual development of apnea. Simultaneous loss of protective airway reflexes highlights the requirement for advanced ventilatory management skills. Serum fentanyl concentrations of 3.0 ng/mL typically produce these latter effects in opioid-naive patients. Miosis is a common side effect and may be used diagnostically to identify both compliance

and overdose. Gastrointestinal effects, dyspnea, and pruritis can be discomforting.The rigid chest syndrome associated with fentanyl infusion is not well described with the transdermal fentanyl device. This may be related to the slower rate of rise of the serum levels with transdermal fentanyl devices than with IV infusion. Mydriasis, vomiting and diarrhea, and piloerection may be used to identify opioid withdrawal***(Sabatowski et al., 2001).***

SIDE-EFFECTS AND TOXICOLOGY

Fentanyl's major side effects (more than 10% of patients) include diarrhea, nausea, constipation, dry mouth, somnolence, confusion, asthenia (weakness), and sweating and, less frequently (3 to 10% of patients), abdominal pain, headache, fatigue, anorexia and weight loss, dizziness, nervousness, hallucinations, anxiety, depression, flu-like symptoms, dyspepsia (indigestion), dyspnea (shortness of breath), hypoventilation, apnea, and urinary retention. Fentanyl use has also been associated with aphasia. Despite being a more potent analgesic, fentanyl tends to induce less nausea, as well as less histamine-mediated itching, in relation to morphine***(Stacey., 2006).***

Like other lipid-soluble drugs, the pharmacodynamics of fentanyl are poorly understood. The manufacturers acknowledge there is no data on the pharmacodynamics of fentanyl in elderly, cachectic or debilitated patients, frequently the type of patient for whom transdermal fentanyl is being used. This may explain the increasing number of reports of respiratory depression events since the late 1970s***(Regnard and Pelham., 2003).***

In 2006 the U.S. Food and Drug Administration (FDA) began investigating several respiratory deaths, but doctors in the United Kingdom were not warned of the risks with fentanyl until September 2008. The FDA reported in April 2012 that young children had died or become seriously ill from accidental exposure to a fentanyl skin patch**(*FDA, 2012).***

The precise reason for sudden respiratory depression is unclear, but there are several hypotheses:

- Saturation of the body fat compartment in patients with rapid and profound body fat loss (patients with cancer, cardiac or infection-induced cachexia can lose 80% of their body fat).
- Early carbon dioxide retention causing cutaneous vasodilatation (releasing more fentanyl), together with acidosis which reduces protein binding of fentanyl, releasing yet more fentanyl.
- Reduced sedation, losing a useful early warning sign of opioid toxicity and resulting in levels closer to respiratory depressant levels**(*FDA, 2012).***

MANAGEMENT OF FENTANYLTOXICITY

The management of fentanyl poisoning, whether transdermal or another route, should focus on ventilatory support and oxygenation first and foremost. This is most typically provided by bagvalve- mask ventilation, although endotracheal intubation or other measures (e.g., laryngeal mask airway) may be needed in some patients. Although naloxone effectively antagonizes fentanyl at the mu-opioid receptor and may avoid intubation in many, it may be avoided best in mildly-poisoned, nonvomiting, opioid-tolerant patients with adequate

spontaneous ventilation. Patients provided solely supportive care will not awaken immediately, which may not prove satisfactory to the clinical staff.

However, administration of naloxone in conventional (0.4–2 mg) dose to this latter group of patients is associated with fulminant awakening and precipitated opioid withdrawal, with its attendant complications. In addition, recrudescence of an underlying pain syndrome, if present, may be undesirable. Judicious titration, starting at very low doses (e.g., 0.05 mg IV), while providing ventilatory support and oxygenation, may provide a more gradual, and safer, awakening. Failure to arouse with an appropriately- titrated dose of naloxone may signal the presence of an overlooked diagnosis, such as a concomitant exposure or cerebral hypoxia. Due to the high potency of fentanyl, higher-than-conventional doses of naloxone may be required on rare occasions.

Although the transdermal fentanyl device should be immediately removed, this is inadequate monotherapy as the reservoir of fentanyl in the stratum corneum will continue to deliver fentanyl systemically for several hours. Although the skin should be cleansed to remove any external drug, the rapidity of absorption makes the benefit of this questionable. Additionally, cleansing would likely have limited or no effect on removing intradermal fentanyl. The optimal cleansing compound is undefined, and soap and water are likely acceptable. It would be appropriate to completely examine the patient for the presence of an unsuspected transdermal fentanyl device***(Pizon and Brooks, 2004).***

Physiology of pain

We all know the feeling - you stub your toe, burn your finger, bump your head – that instant reaction, PAIN. Pain is our body's warning system that tells us something is wrong, most times it is benign but on other occasions it can rob of us of all the pleasures in life, affecting us as we try to complete the smallest of tasks.

What is truly amazing is how pain travels within the body, that this natural warning system that we sometimes curse when we hit our "funny bone," in a beautifully complex process. And even though the pathway is the same from human to human, how we perceive it is a quite different story. Every person feels pain in enormously different ways, even when suffering identical injuries or illnesses and it is here that modern medicine has found great challenges and successes.

DEFINITION

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage or both. Pain is an unpleasant but very important biological signal for danger. Nociception is necessary for survival and maintaining the integrity of the organism in a potentially hostile environment ***(Scholz andWoolf., 2002).***

In 1979, the International Association for the Study of Pain (IASP) introduced the most widely used definition of pain. The IASP defined pain as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.''***(Merskey and Bugduk., 1994).***

History of Pain

Ancient civilizations understood pain when it was visible, such as a cut or scrape, and recorded their accounts of pain and their treatments on stone tablets. But when pain was internal they related it to magic, demons, and evil thus the responsibility of pain relief, through ceremonies and rites, was left to shamans, priests, and sorcerers.The Greeks (and Romans) were the first to advance the theory that the brain and nervous system have a role in producing the perception of pain – sensation. ***(National Institute of Neurological Disorders and Stroke,2007).***

And they also gave us the word "pain" or Poine, who was the Greek goddess of revenge, who was sent to punish the mortal fools who had angered the gods. The ancient Greek Hippocrates, prescribed chewing willow leaves to women in childbirth for their pain-relieving benefits, and this was the "beginning of aspirin" as willow trees, genus Salix, contains a form of salicylic acid the active ingredient in aspirin. ***(Lallanilla .,2005).***

During the 17th and 18th centuries, the French philosopher Rene Descartes (1664) was the first to describe how pain traveled within the body, now called the pain pathway. He illustrated how particles of fire come into contact with the foot, the sensation traveling to the brain and then he compared pain sensations to the ringing of a bell. It was the 19th century that pain came to dwell under a new domain and huge advances in pain therapy. Physicians discovered that pharmaceuticals, such as opium, morphine, codeine, and cocaine, could be used in pain relief. In addition to these drugs, minerals such as gold and ivory were added to various remedies in order to treat various pain-related illnesses.

Another significant discovery was the use of anesthesia for surgery, prior to that physicians used some fairly unusual techniques, such as putting a wooden bowl over a patient's head and hammering on the bowl until the patient passed out. Or they would hold a patient's head over a gas stove, thus inhaling the gas, and wait until they lost consciousness. But it was Queen Victoria who popularized anesthesia – chloroform – for childbirth she actually made it fashionable. ***(Lallanilla 2005)***

NOCICEPTION

The term nociception, which is derived from noci (Latin for harm or injury) is used only to describe the neural component to traumatic or noxious stimuli. All nociception produces pain, but not all pain results from nociception (***Dennis et al., 2001)***.

Significant insights into the cellular and molecular basis of cutaneous nociception have been realized from studies on conscious humans and surrogate animal models, although we are far from understanding the cell biology of pain perception. Advances are hampered by the difficulties inherent in studying neuronal processes in humans, cellular changes in nociceptors induced by invasive
methods, the inability to record directly from the tiny structures where transduction of noxious stimuli occurs, and the uncertainty in model systems that an animal's behavior is due to its perception of pain ***(Le Bars et al., 2001).***

Although the morphology of sensory nociceptive nerve endings is highly conserved in animals from rodents to humans, cutaneous nociceptors are an extremely heterogeneous group of neurons housed in peripheral sensory ganglia located just outside the CNS that transduce external

noxious stimuli in the skin, up to meters away from their cell bodies***(Mense ., 2008).***

Nociceptors often are classified by their conduction velocities, structure, and spinal projections ***(Takahashi et al., 1998).*** Nociceptors have poorly differentiated terminals, slow conduction velocities (C fibers, < 2.5 m s-1 A-δ-fibers, 2.5–20.0 m s-1) and are normally activated by potentially damaging or damaging stimuli, that is, stimuli of strong to noxious intensity ***(Grubb, 1998).***

Physiology of Pain

Pain sensation is a product of several interacting neural systems. Afferent transmission relies on a balance in the activity of both the pain fibers and large proprioceptive or mechanosensory fibers. Inhibitory interneurons are spontaneously active and inhibit projection neurons. Pain transmission can also be modulated by descending pathways that constitute the "analgesia" system.

Peripheral and central connections between sensory neurons and spinal dorsal horn cells occur early in fetal life. Neonates have the same number of pain nerve endings per square millimeter of skin as adults. They are present in fetal mucous membranes and in the skin within the second trimester. Synapses between sensory neurons and spinal interconnections start to develop by 3 months and are complete by the onset of the third trimester. The central nervous system tracts that subserve pain are completely myelinated by 30 weeks. Cortical interconnections with the thalamus, those tracts that play a role in higher perception of pain, are complete by 24 weeks. The descending inhibitory controllers of pain, though, are deficient in the neonate. This leads to the likelihood that

neonates, particularly preterm neonates, may be more sensitive to pain than older children and adults***(Scanlon ., 1991).***

CL A S S I F I C ATION OF PAIN

Although pain classes are not diagnoses, categorizing pain helps guide treatment. Multiple systems for classifying pain exist. These include multidimensional classification systems, such as the IASP Classification of Chronic Pain, and a variety of systems based on a single dimension of the pain experience. Of the latter systems, those based on pain duration (i.e., acute vs. chronic pain) and underlying pathophysiology (i.e., nociceptive vs. neuropathic pain) are used most often. This explores the distinction between acute and chronic pain. It also reviews elements of a mixed pain classification system in which pain is categorized as acute pain, cancer pain, or chronic noncancer pain (CNCP) ***(Merskey and Bugduk., 1994).***

1. Acute Pain

Acute pain was once defined simply in terms of duration. It is now viewed as a "complex, unpleasant experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma." In contrast to chronic pain, relatively high levels of pathology usually accompany acute pain and the pain resolves with healing of the underlying injury***(Chapman and Nakamura., 1999).*** Acute pain is usually nociceptive, but may be neuropathic. Common sources of acute pain include trauma, surgery, labor, medical procedures, and acute disease states. Acute pain serves an important biological function, as it warns of the potential for or extent of injury. A host of protective reflexes (e.g., withdrawal of a damaged limb, muscle spasm, autonomic

responses) often accompany it. However, the "stress hormone response" prompted by acute injury also can have adverse physiologic and emotional effects. Even brief intervals of painful stimulation can induce suffering, neuronal remodeling, and chronic pain; associated behaviors (e.g., bracing, abnormal postures, excessive reclining) may further contribute to the development of chronic pain. Therefore, increasing attention is being focused on the aggressive prevention and treatment of acute pain to reduce complications, including progression to chronic pain states***(Coda and Bonica., 2001).***

2. Chronic Pain

Chronic pain was once defined as pain that extends 3 or 6 months beyond onset or beyond the expected period of healing. However, new definitions differentiate chronic pain from acute pain based on more than just time. Chronic pain is now recognized as pain that extends beyond the period of healing, with levels of identified pathology that often are low and insufficient to explain the presence and/or extent of the pain. Chronic pain is also defined as a persistent pain that "disrupts sleep and normal living, ceases to serve a protective function, and instead degrades health and functional capability." Thus, unlike acute pain, chronic pain serves no adaptive purpose. Chronic pain may be nociceptive, neuropathic, or both and caused by injury (e.g., trauma, surgery), malignant conditions, or a variety of chronic non-life-threatening conditions (e.g., arthritis, fibromyalgia, neuropathy). In some cases, chronic pain exists de novo with no apparent cause. Although injury often initiates chronic pain, factors pathogenetically and physically remote from its cause may perpetuate it. Environmental and affective factors also can exacerbate and perpetuate chronic pain, leading to disability and maladaptive behavior***(Jacobsen and Mariano.,2001).***

3. Cancer Pain

Pain associated with potentially life-threatening conditions such as cancer is often called "malignant pain" or "cancer pain." However, there is movement toward the use of new terms such as "pain associated with human immunodeficiency virus (HIV) infection" or "pain associated with cancer." (The term "cancer pain" is used

in this monograph for the sake of brevity.) Cancer pain includes pain caused by the disease itself (e.g., tumor invasion of tissue, compression or infiltration of nerves or blood vessels, organ obstruction, infection, inflammation) and/or painful diagnostic procedures or treatments (e.g., biopsy, postoperative pain, toxicities from chemotherapy or radiation treatment). There are several reasons why some experts feel that cancer pain merits a discrete category. First, its acute and chronic components and multiple etiologies make it difficult to classify based on duration or pathology alone. Second, cancer pain differs from chronic noncancer pain (CNCP) in some significant ways (e.g., time frame, levels of pathology, treatment strategies). However, there is little evidence to support a distinction between these pain types based on underlying neural processes. Therefore, many pain experts categorize cancer pain as acute or chronic pain***(Turk and Okifuji., 2001).***

4. Chronic Noncancer Pain

A subtype of chronic pain is CNCP, which refers to persistent pain not associated with cancer. In contrast to patients with chronic cancer pain, patients with CNCP often report pain levels that only weakly correspond to identifiable levels of tissue pathology and/or respond poorly to standard treatments. As CNCP may last for many years, some consider use of the traditional term for such pain, "chronic nonmalignant pain," inappropriate. Thus, there is movement toward use of alternate terms such

as "chronic noncancer pain" and "chronic noncancer- related pain." Causes of CNCP include acute injury that has proceeded to chronic pain (e.g., whiplash) and various chronic conditions. In some cases, there is no discernable cause, and the pain is considered the disease. CNCP can affect virtually any body system or region, and pain severity ranges from mild to excruciating. Some types of CNCP have well-defined characteristics and patterns, whereas others do not. Neuropathic and myofascial CNCP can be particularly hard to diagnose, as they may occur in the absence of a known injury or disease process. Because of its chronicity and impact on daily activities, patients with CNCP may experience vocational, interpersonal, and/or psychological problems. If the symptoms of CNCP consume the attention of and incapacitate the patient, he or she may suffer from a psychosocial disorder known as "chronic pain syndrome" (CPS). The pain experienced by these patients is real, and not all patients with CNCP develop this syndrome. Appropriate management of both CNCP and CPS requires an interdisciplinary approach that addresses the complex interaction of physical, psychological, and social factors that contribute to the ongoing pain***(Jacobsen and Mariano.,2001).***

Pain pathways

Pain is conducted along three-neuron pathways that transmit noxious stimuli from the periphery to the cerebral cortex this process by which information about tissue damage is conveyed to the central nervous system (CNS). Exactly how this information is ultimately perceived as painful is unclear. In addition, there can be pain without nociception (e.g.,

phantom limb pain) and nociception without pain. But classic descriptions of pain typically include four processes:

- *Transduction:* the conversion of the energy from a noxious thermal, mechanical, or chemical stimulus into electrical energy (nerve impulses) by sensory receptors called nociceptors
- *Transmission:* the transmission of these neural signals from the site of transduction (periphery) to the spinal cord and brain
- *Perception:* the appreciation of signals arriving in higher structures as pain
- *Modulation*: descending inhibitory and facilitory input from the brain that influences (modulates) nociceptive transmission at the level of the spinal cord***(Pasero et al., 1999).***

Transduction

a. Nociceptor activation and sensitization

Nociceptors are sensory receptors that are preferentially sensitive to tissue trauma or a stimulus that would damage tissue if prolonged. These receptors are the free endings of (primary afferent) nerve fibers distributed throughout the periphery (Figure 13). Signals from these nociceptors travel primarily along two fiber types: slowly conducting unmyelinated C-fibers and small, myelinated, and more rapidly conducting Adelta fibers (Figure 14).

Injury to tissue causes cells to break down and release various tissue byproducts and mediators of inflammation (e.g., prostaglandins, substance P, bradykinin, histamine, serotonin, cytokines). Some of these substances activate nociceptors (i.e., cause them to generate nerve impulses) and most sensitize nociceptors (i.e., increase their excitability and discharge frequency). Ongoing activation of nociceptors may cause nociceptive pain. Peripheral (nociceptor) sensitization amplifies signal

transmission and thereby contributes to central sensitization and clinical pain states***(Byers and Bonica., 2001).***

b. Peripheral neuropathic pain

Not all pain that originates in the periphery is nociceptive pain. Some neuropathic pain is caused by injury or dysfunction of the peripheral nervous system (i.e., peripheral nerves, ganglia, and nerve plexi)(Figure 13) ***(Chapman and Nakamura., 1999).***

c. Clinical implications

Some analgesics target the inflammatory process that produces sensitization. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), thus decreasing the synthesis of prostaglandins. Other analgesics (e.g., antiepileptic drugs, local anesthetics) block or modulate channels, thus inhibiting the generation of nerve impulses.

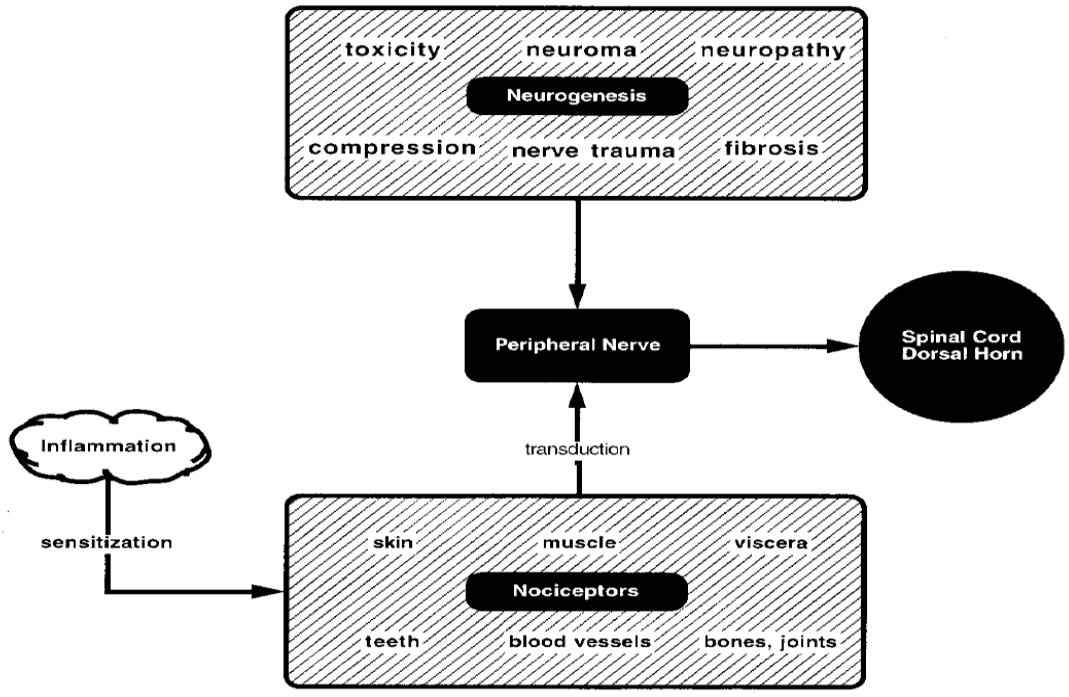


Fig. 13. *Peripheral origins of pain*. Noxious signaling may result from either abnormal firing patterns due to damage or disease in the peripheral nerves or stimulation of nociceptors (free nerve endings due to tissue trauma). Inflammation in injured or diseased tissue sensitizes nociceptors, lowering their firing thresholds. Some clinical pain states have no peripheral origin, arising from disorders of brain function.***(Chapman and Nakamura., 1999).**

Transmission

Nerve impulses generated in the periphery are transmitted to the spinal cord and brain in several phases:21,31

a. Periphery to the spinal cord

Most sensory nerve impulses travel via the nerve processes (axons) of primary afferent neurons to the dorsal horn (DH) of the spinal cord (Figure 14). There, primary afferent neurons propagate nerve impulses to DH neurons through the release of excitatory amino acids (EAAs) (e.g., glutamate, aspartate) and neuropeptides (e.g., substance P) at synapses (connections) between cells. Activated DH projection neurons forward nociceptive impulses toward the brain. However, not all events in the DH facilitatenociception. Spinal interneurons release inhibitory amino acids (e.g., γ-aminobutyric acid [GABA]) and neuropeptides (endogenous opioids) that bind to receptors on primary afferent and DH neurons and inhibit nociceptive transmission by presynaptic and postsynaptic mechanisms. Descending inhibitory input from the brain also modulates DH nociceptive transmission (**Figure 15**). Thus, nociceptive traffic in the DH is not merely relayed to higher centers but rather is heavily modulated. These inhibitory events are part of a natural nociceptive-modulating system that counterbalances the activity of the nociceptive-signaling system***(Terman and Bonica., 2001).***

b. Spinal cord to the brain

The nerve processes of DH projection neurons project to the brain in bundles called ascending tracts. Projection neurons from some DH regions transmit nociceptive signals to the thalamus via the spinothalamic tract (STT) .Others transmit nociceptive information to the reticular formation, mesencephalon, and hypothalamus via the spinoreticular,

spinomesencephalic, and spinohypothalamic tracts (Figure 16) ***(Terman and Bonica., 2001).***

c. Clinical implications

Some analgesics inhibit nociception in theDH. For example, opioid analgesics bind to opioid receptors on primary afferent and DH neurons and mimic the inhibitory effects of endogenous opioids. They also bind to opioid receptors in the brain and activate descending pathways that further inhibit DH nociceptive transmission. Baclofen, a GABA agonist, binds to GABAB receptors and mimics the inhibitory effects of GABA on nociceptive transmission***(Portenoy ., 1996).***

Perception

The perception of pain is an uncomfortable awareness of some part of the body, characterized by a distinctly unpleasant sensation and negative emotion best described as threat. Both cortical and limbic system structures are involved. Nociceptive information from some DH projection neurons travels via the thalamus to the contralateral somatosensory cortex , where input is somatotopically mapped to preserve information about the location, intensity, and quality of the pain. The thalamus relaysother nociceptive input to the limbic system. This input joins input from the spinoreticular and spinomesencephalic tracts to mediate affective aspects of pain. Immediate social and environmental context influences the perception of pain, as do past experience and culture. Consequently, a standard cause of pain (e.g., surgery) can generate enormous individual differences in pain perception***(Chapman., 2001).***

Modulation

a. Descending pathways

Modulation of nociceptive transmission occurs at multiple (peripheral, spinal, supraspinal) levels. Yet, historically, modulation has been viewed as the attenuation of DH transmission by descending inhibitory input from the brain. Melzack and Wall's Gate Control Theory brought this notion to the forefront in 1965. Models of descending pain systems now include both inhibitory and facilitory descending pathways. Multiple brain regions contribute to descending inhibitory pathways. Nerve fibers from these pathways release inhibitory substances (e.g., endogenous opioids, serotonin, norepinephrine, GABA) at synapses with other neurons in the DH. These substances bind to receptors on primary afferent and/or DH neurons and inhibit nociceptive transmission. Such endogenous modulation may contribute to the wide variations in pain perception observed among patients with similar injuries***(Terman and Bonica., 2001).***

b. Clinical implications

Some analgesics enhance the effects of descending inhibitory input. For example, some antidepressants interfere with the reuptake of serotonin and norepinephrine at synapses, increasing their relative interstitial concentration (availability) and the activity of endogenous pain-modulating pathways. Thus, some, but not all, antidepressants are used to treat some types of chronic pain***(Wallace., 1992).***

Peripheral Sensitization

Inflammatory mediators, intense, repeated, or prolonged noxious stimulation, or both can sensitize nociceptors. Sensitized nociceptors exhibit a lowered threshold for activation and an increased rate of firing. In other words, they generate nerve impulses more readily and more

often. Peripheral (nociceptor) sensitization plays an important role in central sensitization and clinical pain states such as hyperalgesia (increased response to a painful stimulus) and allodynia (pain caused by a normally innocuous stimulus)***(Fields et al., 1998).***

Central Sensitization

a. Definitions and features

Central sensitization refers to a state of spinal neuron hyperexcitability. Tissue injury (inflammation), nerve injury (i.e., aberrant neural input), or both may cause it, and ongoing nociceptive input from the periphery is needed to maintain it. Repeated stimulation of Cnociceptors initially causes a gradual increase in the frequency of DH neuron firing known as "wind-up." Activation of N-methyl D-aspartate (NMDA) receptorse plays a key role in this process. The clinical correlate of wind-uptemporalsummation-refers to a progressive increase in pain experienced over the course of a repeated stimulus. Repeated or prolonged input from C-nociceptors or damaged nerves causes a longer-lasting increase in DH neuron excitability and responsiveness (i.e., central sensitizationf) which may outlast the stimulus by minutes to hours***(Covington ., 2000).***

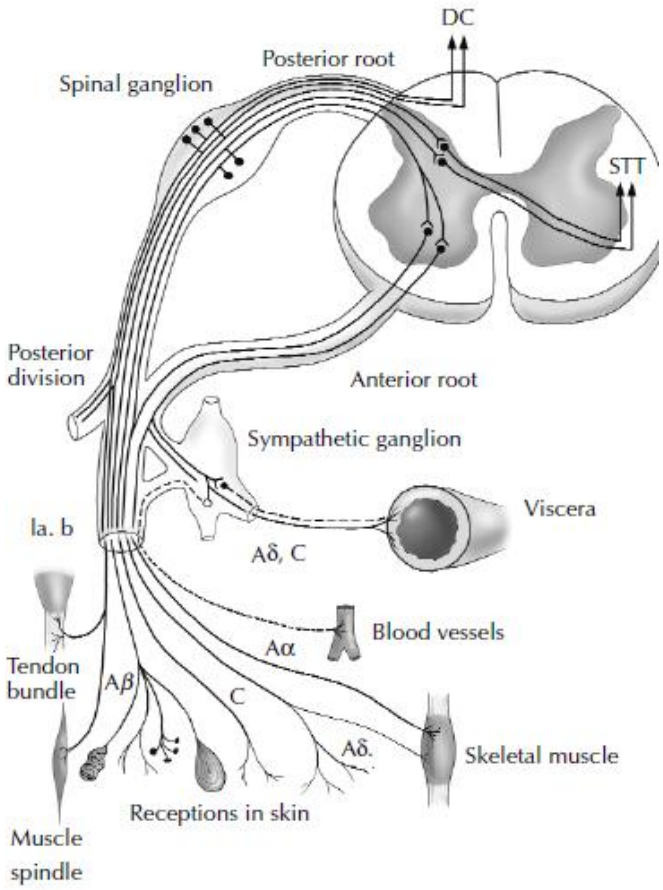
Central sensitization is associated with a reduction in central inhibition, spontaneous DH neuron activity, the recruitment of responses from neurons that normally only respond to lowintensity stimuli (i.e., altered neural connections), and expansion of DH neuron receptive fields. Clinically, these changes may manifest as: 1) an increased response to a noxious stimulus (hyperalgesia), 2) a painful response to a normally innocuous stimulus (allodynia), 3) prolonged pain after a transient stimulus (persistent pain), and 4) the spread of pain to uninjured tissue (i.e., referred pain). In contrast to hyperalgesia caused by peripheral

mechanisms (i.e., primary hyperalgesia), such secondary hyperalgesia extends beyond the region of injury***(Ru-Rong and Woolf .,2001).***

b. Clinical implications

Sensitization is likely responsible for most of the continuing pain and hyperalgesia after an injury. This sensitivity may be due to "normal" noxious input from injured and inflamed tissue or "abnormal" input from injured nerves or ganglia. In the former case, sensitization serves an adaptive purpose. That is, the hyperalgesia and allodynia encourage protection of the injury during the healing phase. However, these processes can persist long after healing of the injury in the setting of chronic pain. Central sensitization plays a key role in some chronic pain, especially pain induced by nerve injury or dysfunction (i.e., neuropathic pain). It explains why neuropathic pain often exceeds the provoking stimulus, both spatially and temporally***(Covington ., 2000).***

Central sensitization also explains the longstanding observation that established pain is moredifficult to suppress than acute pain. In contrast to nociceptive pain, neuropathic pain is often unresponsive or poorly responsive to NSAIDs and opioids. However, it may respond to antiepileptic drugs, antidepressants, or local anesthetics***(Cherny et al., 2004).***



Figu. 14. *A simplified schema of a spinal nerve and the different types of fibers contained therein. (DC: dorsal columns; STT: spinothlamic tract).* ***(Terman and Bonica., 2001).***

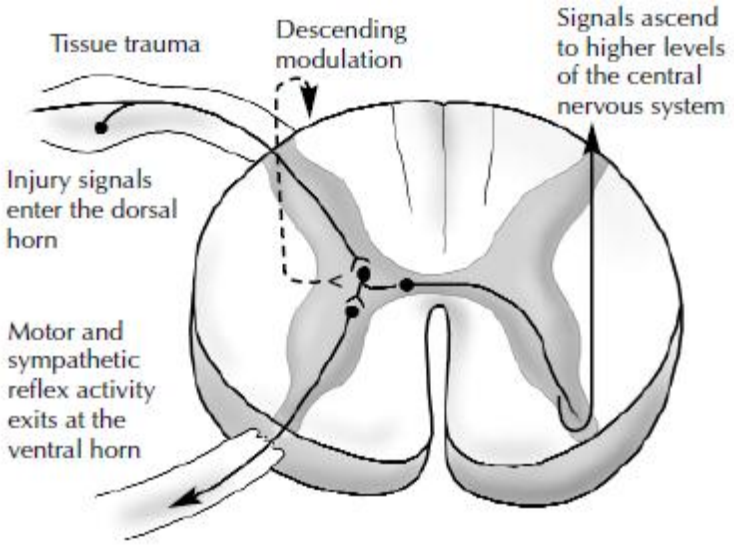


Fig. 15. *A simplified view of spinal cord mechanisms*. Afferents conveying noxious signaling from the periphery enter the dorsal horn of the spinal cord, where they synapse with dorsal horn neurons. This generates nerve impulses that exit the cord ipsilaterally through motor and sympathetic efferents. Other activity produces signals that ascend to various areas in the brain. This simple sketch shows only the

anterolateral funiculus, which ascends to the brain stem and thalamus. Inhibitory influences include certain spinal interneurons and descending pathways from periadqueductal gray and other areas (dashed line).
(Chapman and Nakamura., 1999).

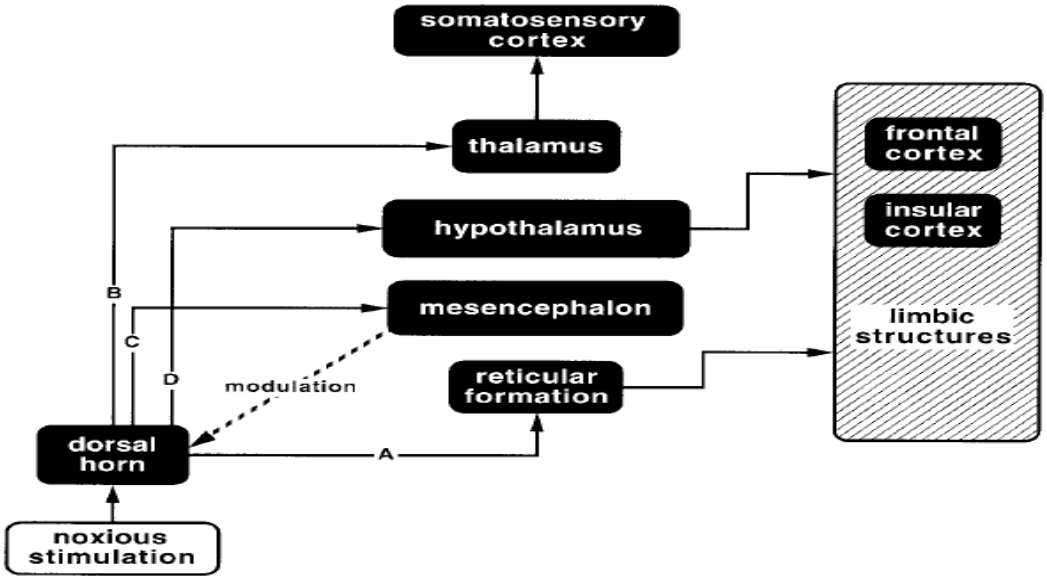


Fig. 16. *Multiple pathways of nociceptive transmission for the spinal cord to central structures. There are four major pathways the A: spinoreticular; B: spinothalamic; C: spinomesencephalic; and D: spinohypothalamic tracts.*
(Chapman and Nakamura., 1999).

Pain in Pediatric

Perhaps one of the most difficult challenges professionally and emotionally is learning to handle pain in pediatric patients. It is sometimes a necessary part of our work to inflict pain during procedures, immunizations, and other treatments. In the past, there was a relative lack of accountability for providing pain relief. The major focus now is on how to properly assess pain. Culture has changed as evidenced by the new Joint Commission on Accreditation of Healthcare Organizations (JCAHO)

regulations. Pain is considered "the fifth vital sign" requiring caregivers to regularly assess and address pain***(McCaffery ., 2003).***

However, pain remains one of the most misunderstood, underdiagnosed, and undertreated/untreated medical problems.An important responsibility of physicians who care for children is eliminating or assuaging pain and suffering when possible. It has been well documented, however, that in this regard a substantial percentage of children have been undertreated. The most common type of pain experienced by children is acute pain resulting from injury, illness, or, in many cases, necessary medical procedures. There is extensive literature that describes how to evaluate and treat acute pain in children using low-cost, widely available, convenient, and safe methods; this information, however, has not been readily applied***(Schechter et al., 2004).***

Although this statement focuses on acute pain, it is the obligation of primary care physicians, general pediatricians, pediatric surgeons, and pediatric subspecialists to recognize and address all types of pain, including acute pain, chronic pain, recurring pain, procedure-related pain, and pain associated with terminal illness. The American Academy of Pediatrics (AAP) and the American Pain Society (APS) jointly issue this

statement to underscore the responsibility of pediatricians to take a leadership and advocacy role to ensure humane and competent treatment of pain and suffering in all infants, children, and adolescents. A major aim of pain treatment is to eliminate painassociated suffering. Pain is an inherently subjective experience and should be assessed and treated as such. Pain has sensory, emotional, cognitive, and behavioral components that are interrelated with environmental, developmental, sociocultural, and contextual factors. Suffering occurs when the pain leads the person to feel out of control, when the pain is overwhelming, when the source of the pain is unknown, when the meaning of the pain is perceived to be dire, and when the pain is chronic. The concepts of pain and suffering go well beyond that of a simple sensory experience***(Cassell.,2007).***

Pain is a common reason for paediatric patients to present to hospital. Pain can have a direct impact on health outcomes and, if uncontrolled, may have a diverse effect on all areas of life. This is because pain is not only a sensory perception but has emotional, cognitive, and behavioural components, which also need to be recognised. The impact and perception of pain is also influenced by a patients' individual developmental, environmental, and sociocultural background. If pain is not adequately managed acutely there is good evidence suggesting that untreated pain may have long-term negative effects on pain sensitivity, immune functioning, neurophysiology, attitudes, and health care behaviour. It is therefore essential that health care professionals looking after children of all ages are trained to recognise and treat pain whether it be acute or chronic. Good quality, effective management of pain in paediatric patients is therefore an essential component of paediatric anaesthesia. However, achieving this can be difficult for a variety of

reasons not least of which is the enormous variations that occur physiologically and psychologically throughout the range of ages encountered in the paediatric population. Firstly, some of the developmental neurobiological issues will be considered***(Cassell.,2007).***

DEVELOPMENT OF PAIN PATHWAYS

All neural pathways required for nociception are present from birth and are also functional in premature neonates. However, many molecules, neurotransmitters and receptor-mediated systems are variably expressed depending upon developmental age. As a result, a noxious stimulus may provoke different patterns of activity dependent on the stage of maturity of the paediatric central nervous system.

In the peripheral nervous system, C-fibres are mature in neonates although their cortical connections at the level of the dorsal horn are immature. However, interestingly, at the same stage A-Beta fibres show extended connections within the spinal cord that can produce nociceptive signalling from lower intensity stimuli. These A-Beta fibres only recede once C-fibres have matured. The result of this observation is that there is far less discrimination between the perception of noxious and non-noxious stimuli in the paediatric patient. Furthermore, and of added clinical importance, is that inhibitory pathways are not fully developed in the spinal cord during early life. The combination of widened receptive fields, lower sensory discrimination and reduced inhibitory pathways results in the immature nervous system in paediatric patients experiencing *more* pain in response to noxious stimuli and not less as was previously believed***(Young., 2005).***

PAEDIATRIC PAIN ASSESSMENT TOOLS

Systematic, routine pain assessment using standardized, validated measures is accepted as the foundation of effective pain management for patients, regardless of age, condition or setting. The assessment tools are based on either self-report or observation of behaviour. Self-report is the only truly direct measure of pain and hence it is considered the 'gold standard' of measurement. However, no single tool can be used for pain assessment across all children or all cases. Therefore, healthcare professionals need to be not only trained in the use of pain assessment tools but also need to be aware of their limitations. If performed successfully, accurate assessment of pain is associated with improvements not only in pain management but also in patient, parent and staff satisfaction. However, despite these benefits pain in paediatric patient is often infrequently assessed***(Franck and Bruce ., 2009).***

Recommendations made by the Royal College of Nursing are to anticipate pain wherever possible and be vigilant for any indications of pain in the paediatric patient. Children's self-report of pain is the preferred method but when this is not possible an appropriate behavioural or composite tool should be used. Indicators that point to the presence of uncontrolled pain include changes in physiological signs such as heart rate, respiratory rate, blood pressure, intracranial pressure and sweating while other important observations include changes in a child's behaviour, appearance or activity level. However, no individual tool can be broadly recommended for pain assessment in all children and across all contexts. It is important to assess, record, and re-evaluate pain at regular intervals; the frequency of which should be determined according to the individual needs of the child and setting. Be aware that language,

ethnicity and cultural factors may influence the expression and assessment of pain***(Royal College of Nursing (UK), 2009).***

A number of formal means of assessment of paediatric pain are available. Some of these are summarised below and can be divided into self-report and observational.

Self-report

Visual analogue scale (VAS) -Self-report visual analogue scales for pain intensity. It is a horizontal line with "no pain" at one end to "worst possible pain" at the other. Patient draws a line that intersects to indicate intensity. For ages 3- adult.

Fig. 16. *Visual analogue scale (VAS) This scale incorporates a visual analogue scale, a descriptive word scale and a colour scale all in one tool.*

Wong-Baker Faces Pain Rating Scale - Self-report faces scale for acute pain. Six line-drawn faces range from no pain to worst pain. It assigns a numerical value to each face. The Wong-Baker Scale also adds word descriptors to each face (no hurt, hurts a little, hurts a whole lot, etc.) Age group 3-18 years***(Wong and Baker., 1988).***

Faces Pain Scale-Revised (FPS-R) - Self-report faces scale for acute pain. Six cartoon faces range from neutral to high pain expression. These faces can be numbered 0, 2, 4, 6, 8, and 10. Age group 4- 16 years.

Fig. 17. *Facial pain scale.*

(Hicks et al., 2001).

Poker chip tool - Self-report poker chips are used to represent pain intensity. Child chooses which chips represent the pain they experience with one chip indicating a little hurt and all four chips indicating the most hurt a child could have. Age group 4-7 years***(Hester., 1979).***

Observational

FLACC Pain Assessment Tool which incorporates five categories of pain behaviours (Face, Legs, Activity, Cry and Consolability) Scale is a behavioral scale that has been validated for assessment of postoperative pain in children between the ages of 2 months and 7 years. After observing a child for one to five minutes, a pain score is obtained by reviewing the descriptions of behavior and selecting the number that most closely matches the observed behavior.

FLACC Behavioral Pain Assessment

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry, (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching hugging or being talked to, distractible	Difficulty to console or comfort

Each of the five categories is scored from 0-2, resulting in a total score between 0 and 10.***(Merkle et al., 1997).***

Procedure Behavior Checklist (PBCL). Observational measure of pain and anxiety during invasive medical procedures. The behaviours assessed in the PBCL include muscle tension, screaming, crying, restraint used, pain verbalized, anxiety verbalized, verbal stalling and physical

resistance. Eight operationally defined behaviours rated on occurrence and intensity (scale 1–5).Age group 3-18 years.

(Katz et al., 1980).

Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). Observational measure of postoperative pain in children. The CHEOPS assesses six behaviours that include cry, facial, child verbal, torso, touch and legs. Each behaviour is coded on a scale of 0 to 3 based on intensity. Age group 1–12 years***(McGrath et al., 1985).***

COMFORT Scale. Observer rated measure for use in intensive care environments. The COMFORT scale assesses eight domains thought to be indicative of pain and distress including alertness, calmness/agitation, respiratory response, physical movement, mean arterial blood pressure, heart rate, muscle tone and facial tension. Each dimension is scored between 1 and 5, and the scores are added to yield a measure of sedation. Age group 0–18 years***(Ambuel et al., 1992).***

Pediatric sedation

Sedation of pediatric patients has serious associated risks, such as hypoventilation, apnea, airway obstruction, laryngospasm, and cardiopulmonary impairment. These adverse responses during and after sedation for a diagnostic or therapeutic procedure may be minimized, but not completely eliminated, by a careful preprocedure review of the patient's underlying medical conditions and consideration of how the sedation process might affect or be affected by these conditions***(Hoffman et al., 2009).***

DISCHARGE CRITERA

Patients should be discharged only when they have met specific criteria – this should be consistent regardless of the procedure that was performed

or the drugs that were used for sedation. The criteria for discharge should include: 1) stable vital signs 2) pain under control 3) a return to the level of consciousness that is similar to the baseline for that patient 4) adequate head control and muscle strength to maintain a patent airway 5) Nausea and/or vomiting should be controlled and the patient should be adequately hydrated. Recent data suggest the importance of discharge criteria being time based, (e.g. patients must maintain wakefulness for ≥ 20 miniutes)***(Coté and Wilson., 2006).***

Sedation scores

The ability to determine the level of sedation in the pediatric population is a challenge for the bedside nurse. There are a number of different tools to assist the bedside nurse. The three most frequently used in the pediatric population are (1) the Ramsey Scale, (2) the Comfort Scale, and (3) the University of Michigan Sedation Scale (UMSS). The Ramsey Scale was developed in the early 1970s and validated using an adult population and measures anxiety level from agitated and anxious to no response on a scale from 1 to 6. The higher the score the more sedate the patient . The Comfort Scale was developed initially in the 1960s and revised in the 1980s specifically for the pediatric ICU population by Ambuel . The scale measures eight domains that include alertness, agitation level, respiratory response, physical movement, blood pressure, heart rate, muscle tone, and facial tone, with five sublevels for each domain ***(De Jonghe et al., 2005).***

The lower the score the more sedate the child. The reported Cronbach's alpha is 0.9 and a correlation coefficient of 0.75 to 0.84. The UMSS was designed for use in determining level of sedation for procedures in a pediatric population but also has been used in the PICU . The scale has five levels from awake to unarousable with a higher score indicative of

deeper sedation . The validation data for the PICU are lacking but the reported kappa score of agreement is 0.59 to 0.84 in children undergoing sedation during invasive procedures***(Malviya et al., 2006).***

Tab. 2. *Modified Ramsay scale* ***(Ramsay et al. 1974).***

Level	Characteristics
1	Anxious, agitated, restless
2	Awake, cooperative, oriented, tranquil
3	Semiasleep but responds to commands
4	Asleep but responds briskly to glabellar tap or loud auditory stimulus
5	Asleep with sluggish or decreased response to glabellar tap or loud auditory stimulus
6	No response can be elicited

A score of 2 to 3 is anxiolysis, 4 to 5 is moderate sedation, 6 is deep sedation

Patients and Methods

This study was conducted on 80 children aged between 1 and 5years old, ASA grade I of both sexes. All children were scheduled for elective distal penile hypospadius repair and uncomplicated right and left congenital inguinal hernia repair surgeries. Exclusion criteria included children with bleeding diathesis, Neuromuscular or spinal diseases. Children with back problems and local skin infections of the caudal area. Children with mental retardation or delayed development. Known allergy to the used drugs. As determined by pre-operative evaluation. All cases were done in Benha Children Hospital and Benha University Hospitals after approved consent of the parents.

Patients were randomly assigned for one of four groups, each group composed of **20** patients, according to the type of caudally injected drug.

Group1(CB) caudal bupivacaine 1ml/kg(0.125%)(control group).

Group2(CD)caudal bupivacaine 1ml/kg(0.125%)+ dexmedetomidine(2 µg/kg).

Group3 (CF) caudal bupivacaine 1ml/kg(0.125%)+fentanyl (2 µg/kg).

Group4(CC) caudal bupivacaine1ml /kg(0.125%)+ clonidine(2 µg/kg).

Anesthetic technique:

I- Preoperative preparation:

All patients were ASA I, Fasting hours were Clear liquids 2 h, Breast milk 4 h, Infant formula 6 h, Nonhuman milk 6 h, Light meal 6 h. No premedications as benzodiazepines or Opioids were given so as not to interfere with our results.

II- Induction of anesthesia:

Patients in all groups received a standard anesthetic technique. Anaesthesia will be induced with halothane in oxygen 100%. An i.v. cannula will be inserted after alcohol sterilization and routine administration of atropine (0.01- 0.02 mg/kg) will be given. After induction of anaesthesia, laryngeal mask with appropriate size according to body weight will be inserted.

III- Maintenance of anesthesia:

Anesthesia was maintained with 1.5– 2% halothane in.oxygen 100% and spontaneous ventillation with the use of Ayres T piece. Routine vital function monitoring of the blood pressure, ECG, oxygen saturation, end-tidal carbon dioxide were continuously displayed and recorded every 5 minutes till the end of surgery and the mean value of each parameter were analysed . No sedatives, Opioids or analgesics were given intra-operatively.

Then the patient was put in the left lateral position, with flexed hips and knees and good observation of the respiratory pattern and the transmitted inflation and deflation of the bag. After complete sterilization, caudal analgesia was performed using 22-gauge needle guided by 2 sacral cornu and tip of coccyx, after negative aspiration to ensure no blood or CSF, the drug was injected according to each group. After the end of caudal technique, the patient was replaced in the supine position. And surgery will

be planned to be started after 15 minutes. At the end of the surgery removal of the laryngeal mask after adequate oral suction while the patient is anesthetized and oral airway was inserted after closure of the vaporizer. After full recovery from general anesthesia, patients were transferred to the recovery room with continuous monitoring of vital data.

IV- Postoperative assessment:

All patients were observed in the recovery room for 30 min. before transferring to the ward. The following parameters were recorded at 30min., 1h, 2h, 3h, 4h, 6h, and 12h postoperative:

1. Heart rate.
2. Arterial blood pressure(systolic and diastolic).
3. O_2 saturation.
4. Respiratory rate.
5. Quality of analgesia: This was assessed using FLACC score(Tab. 3).
6. Measurement of sedation score using Modified Ramsay scale(Tab. 4).
7. Time to the 1st analgesic request. (I.e. at which analgesia in the form of IV pethidine will be needed).
8. Post anesthetic side effects, if any, were reported as:
   a) Nausea.
   b) Vomiting and if happen ondanesteron given.
   c) Urinary retention if happen catheterization done.
   d) Pruritus if happen diphenhydramine given.

FLACC score (Face, Legs, Activity, Cry and Consol ability-scale) (FLACC).

Tab. 3. *FLACC score**(Merkel et al., 1997)***.

	Scoring		
Categories	**0**	**1**	**2**
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Note: Each of the five categories Face (F), Legs (L), Activity (A), Cry (C), and Consolability (C) is scored from 0-2, which results in a total score between 0 and 10.

score ranges from 0 to 10. 0–3 = mild, 4–6 = moderate, 7–10 = severe pain. Score of ≥3 represents pain.

Tab. 4 ***Modified Ramsay Scale (Ramsay et al. 1974).***

Level	**Characteristics**
1	Anxious, agitated, restless
2	Awake, cooperative, oriented, tranquil
3	Semiasleep but responds to commands
4	Asleep but responds briskly to glabellar tap or loud auditory stimulus
5	Asleep with sluggish or decreased response to glabellar tap or loud auditory stimulus

6	No response can be elicited

A score of 2 to 3 is anxiolysis, 4 to 5 is moderate sedation, 6 is deep sedation.

Statistical analysis :

The collected data were tabulated and analyzed using SPSS version 16 soft ware (SpssInc, Chicago, ILL Company). Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation, range. Chi square test (X^2), and ANOVA (analysis of variance) were used as tests of significance. The accepted level of significance in this work was stated at 0.05 (P <0.05 was considered significant).

P value >0.05 insignificant

P<0.05 significant

P<0.001 highly significant

Results

The study compared 80 patients divided into four groups. Each consists of 20 patients according to the caudally injected drug. The study compared the analgesic , sedative and hemodynamic effects of bupivacaine alone, fentanyl, bupivacaine with dexmedetomidine and bupivacaine with clonidine when injected caudally.

The demographic data:

The demographic data of the study groups are shown in (Tab 5 &6). There were no statistically significant differences between the four groups as regards age, weight, sex, type and duration of operation.

Tab. 5.Comparing the studied groups regarding age, weight, Sex, Duration of operation, No of patients

Intra-operative data	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
Age	2.68	0.838	3.27	0.935	3.28	1.205	3.27	1.060	1.71	0.17
Weight	13.5450	2.48860	14.6500	1.95408	14.2250	2.80261	14.6250	3.26414	0.75	0.52
Sex (M:F)	14:6		17:3		15:5		16:4			
Duration of operation	63.6500	5.9760	62.3000	4.3420	63.5500	3.7343	64.2500	3.5670	0.6604	0.5780

Tab. 6.Comparing the studied groups regarding type of operation

Intra-operative data	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
type of operation	1.0000	0.8584	1.0500	0.8256	0.9000	0.8522	1.0000	0.7947	0.1141	0.9518

The intra operative data(Table 7):

The intraoperative data include the heart rate, the blood pressure(systolic and diastolic), respiratory rate, oxygen saturation and end tidal CO_2

As regards the heart rate :

- **Group 1**[Caudal Bupivacaine(**CB**)] it has the highest value with mean(114.3 ± 13.20b/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2**[Caudal Bupivacaine with dexmedetomidine(**CD**)] follow **Group 1** with mean (95.85 ± 18.27 b/m) which is highly significant difference(P<0.001) compared with the other two groups **Group 3 and Group 4.**
- **Group 3**[Caudal Bupivacaine with fentanyl(**CF**)] **and Group 4**[Caudal Bupivacaine with clonidine(**CC**)] have the lowest values with means(89.25 ± 17.06 &89.5 ± 17.89 b/m) respectively which is statistically highlysignificant difference(P<0.001).

As regards the systolic blood pressure:

- **Group 1** (**CB**) it has the highest value with mean(94.85 ± 9.86 mmHg) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** (**CD**) follow **Group 1** with mean (90.65 ± 7.48 mmHg) which is highly significant difference(P<0.001) compared with the other two groups **Group 3 and Group 4.**
- **Group 3** (**CF**) **and Group 4** (**CC**) have the lowest values with means(83.95 ± 8.57&88.95 ± 6.95 mmHg) respectively which are statistically highly significant difference(P<0.001).

As regards the diastolic blood pressure:

- **Group 1** (**CB**) it has the highest value with mean (64.3 ± 7.26mmHg) which is highly significant difference (P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** (**CD**) follow **Group 1** with mean (51 ± 4.26mmHg) which is highly significant difference (P<0.001) compared with the other two groups **Group 3 and Group 4.**
- **Group 3** (**CF**) **and Group 4** (**CC**) have the lowest values with means(48.5 ± 4.2 & 49.55 ± 5.52 mmHg) respectively which are statistically highly significant difference (P<0.001).

As regards the respiratory rate:

- **Group 1** (**CB**) it has the highest value with mean(26.35 ± 4.58br/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** (**CD**) **and Group 4** (**CC**) follow **Group 1** with mean (23.8 ± 3.75 & 22.45 ± 3.14 br/m) respectively which are highly significant difference(P<0.001) compared with **Group 3**
- **Group 3** (**CF**) has the lowest value with mean (17.35 ± 2.68 br/m) respectively which is statistically highly significant difference(P<0.001).

As regards the oxygen saturation: there is no statistically significant difference among the four groups

As regards the end tidal co_2:

- **Group 3** (**CF**) it has the highest value with mean(38.4 ± 3.86 mmHg) which is highly significant difference(P<0.001) compared with the other three groups **Group 1, Group 2 and Group 4.**
- **Group 4** (**CC**) **and Group 2** (**CD**) follow **Group 3** with mean (30.15 ± 2.43 & 29.65 ± 4.3 mmHg) respectively which are highly significant difference(P<0.001) compared with **Group 1**
- **Group 1** (**CB**) has the lowest value with mean (25.8 ± 4.07 mmHg) which is statistically highly significant difference(P<0.001).

Tab. 7.Comparing the studied groups regarding the intraoperative HR, SBP, DBP, RR, SPO2, ETCO2

Intra-operative data	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
HR	114.3000	13.20327	95.8500	18.27070	89.2500	17.06605	89.5000	17.88707	9.9	<0.001*
SBP	94.8500	9.85834	90.6500	7.48525	83.9500	8.57460	88.9500	6.95455	9.5	<0.001*
DBP	64.3000	7.25549	51.0000	4.25503	48.5000	4.19900	49.5500	5.51553	32.4	<0.001*
RR	26.3500	4.57999	23.8000	3.75009	17.3500	2.68083	22.4500	3.13679	22.04	<0.001*
SPO2	99.3500	0.4894	99.5500	0.5104	99.3000	0.6569	99.7000	0.4702	2.3714	0.0763
ETCO2	25.8000	4.07302	29.6500	4.29535	38.4000	3.85801	30.1500	2.43386	28.6	<0.001*

The postoperative data:

The heart rate(Table 8):

As regards the heart rate after 30 min. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(114.35 ± 12.53 b/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** (**CD**) follow **Group 1** with mean (95.5 ± 16.78 b/m) which is highly significant difference(P<0.001) compared with the other two groups **Group 3 and Group 4.**
- **Group 3** (**CF**) **and Group 4** (**CC**) have the lowest values with means(88.2 ± 16.31&88.01 ± 16.97 b/m) respectively which are statistically highly significant difference(P<0.001).

As regards the heart rate after 1 hr. postoperatively:

The sme interpretation as in 30 min. postoperative observation.

As regards the heart rate after 2 hrs. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(112 ± 13.7 b/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** (**CD**) and **Group 3**(**CF**) follow **Group 1** with means(88.65 ± 15.22 &87.1 ± 13.43b/m) respectively which are highly significant difference(P<0.001) compared with **Group 4.**
- **Group 4** (**CC**) has the lowest value with mean (81.75 ± 13.67 b/m) which is statistically highly significant difference(P<0.001).

As regards the heart rate after 3 hrs. postoperatively:

The same interpretation as in 2 hrs. postoperative observation.

As regards the heart rate after 4 hrs. postoperatively:

- **Group 1** it has the highest value with mean(109.55 ±14.33 b/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 3** follow **Group 1** with means(89.55 ± 14.92 b/m) which is highly significant difference(P<0.001) compared with **Group 2** and **Group 4.**
- **Group 2** and **Group 4** have the lowest values with means (83.5 ± 15 & 82.75 ± 12.89 b/m) respectively which are statistically highly significant difference(P<0.001).

As regards the heart rate after 6 hrs. postoperatively:

- **Group 1** it has the highest value with mean(108.65 ± 14 b/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** has the lowest value with mean (82.2 ± 15.21 b/m) respectively which are statistically highly significant difference(P<0.001)compared with the other two groups **Group 3 and Group 4.**

As regards the heart rate after 12 hrs. postoperatively:

- **Group 1** it has the highest value with mean(109.1 ± 13.29 b/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**

- **Group 2** has the lowest value with mean (85.1 ± 14.67 b/m) which is statistically highly significant difference(P<0.001)compared with the other two groups **Group 3 and Group 4.**

Tab. 8. Comparing the studied groups regarding HR over the postoperative follow up

HR over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
HR 0.5 hr.	114.35	12.533	95.50	16.775	88.20	16.314	88.01	16.970	12.5	<0.001*
HR 1 hr.	113.25	12.387	94.00	16.886	87.10	14.955	83.30	16.212	15.3	<0.001*
HR 2 hr.	112.00	13.699	88.65	15.218	87.10	13.427	81.75	13.672	19.2	<0.001*
HR 3 hr.	110.00	13.034	85.45	16.372	86.60	14.162	82.65	12.629	15.1	<0.001*
HR 4 hr.	109.55	14.325	83.50	14.992	89.55	14.922	82.75	12.887	12.3	<0.001*
HR 6 hr.	108.65	14.004	82.20	15.209	94.85	15.702	85.00	12.624	9.8	<0.001*
HR 12 hr.	109.10	13.293	85.10	14.671	100.40	15.895	93.90	13.309	9.5	<0.001*

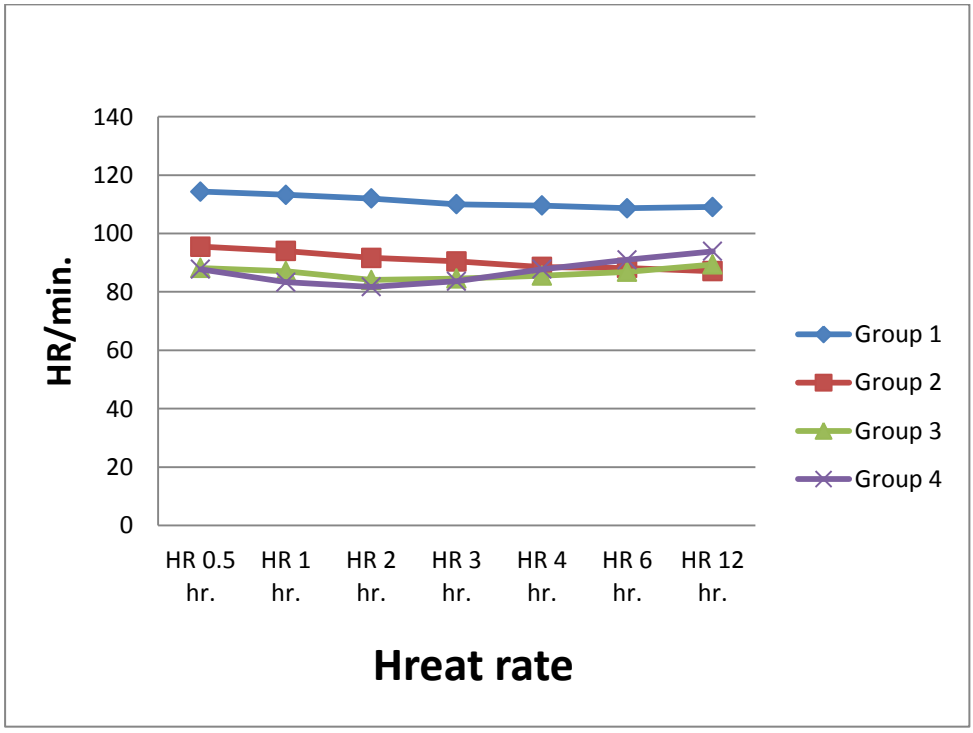


Fig. 18.*Comparing the studied groups regarding HR over the postoperativefollow up*

The systolic blood pressure(SBP) (Table 9):

As regards the SBP after 30 min. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(105 ±10.76 mmHg) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 4** (**CC**) follow **Group 1** with mean (101.55 ± 7.69 mmHg) which is highly significant difference(P<0.001) compared with the other two groups **Group 3 and Group 2.**
- **Group 3** (**CF**) **and Group 2** (**CD**) have the lowest values with means(90.15 ± 9.65 & 94.35 ± 7.26 mmHg) respectively which are statistically highly significant difference(P<0.001).

As regards the SBP after 1 hr. postoperatively:

The same interpretation as in 30 min. postoperative observation.

As regards the SBP after 2 hrs. postoperatively:

- **Group 1** (**CB**) & **Group 4** (**CC**) have the highest values with means(100 ± 12.92 & 99.1 ± 11.1 mmHg) respectively which are highly significant difference(P<0.001) compared with the other two groups **Group 2and Group 3.**
- **Group 3** (**CF**) **and Group 2** (**CD**) have the lowest values with means(89.9 ± 11.59 & 90.75 ± 8.88 mmHg) respectively which are statistically highly significant difference(P<0.001).

As regards the SBP after 3 hrs. postoperatively:

- **Group 1** (**CB**) & **Group 4** (**CC**) have the highest values with means(100.35 ± 14.34 & 100.35 ± 15.644 mmHg) respectively which are significant difference(P<0.01) compared with the other two groups **Group 2and Group 3.**
- **Group 3** (**CF**) follow **Group 1** with mean (90.95 ± 12.83 mmHg) which is significant difference(P<0.01) compared with **Group 2.**
- **Group 2** (**CD**) has the lowest value with mean (88.85 ± 10.72 mmHg) which is statistically significant difference(P<0.01).

As regards the SBP after 4 hrs. postoperatively:

- **Group 1** (**CB**) & **Group 4** (**CC**) have the highest values with means(99.85 ± 14.89 & 100.7 ± 18.82 mmHg) respectively which are significant difference(P= 0.015) compared with the other two groups **Group 2 and Group 3.**

- **Group 3** (**CF**) follow **Group 1** with mean (90.5 ± 14.75 mmHg) which is significant difference(P= 0.015) compared with **Group 2.**
- **Group 2** (**CD**) has the lowest value with mean (87.55 ± 12.22 mmHg) which is statistically significant difference(P= 0.015).

As regards the SBP after 6 hrs. postoperatively:

The same interpretation as in 4 hrs. postoperative observation.

As regards the SBP after 12 hrs. postoperatively: there were no statistically significant difference among the study groups.

Tab. 9.Comparing the studied groups regarding SBP over the postoperative follow up

SBP over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
0.5 hr.	105.00	10.760	94.35	7.264	90.15	9.653	101.55	7.694	5.96	< 0.001*
1 hr.	102.70	11.079	93.20	8.326	90.35	10.678	98.25	7.919	5.9	< 0.001*
2 hr.	100.00	12.924	90.75	8.884	89.90	11.589	99.10	11.097	6.23	< 0.001*
3 hr.	100.35	14.342	88.85	10.722	90.95	12.828	100.35	15.644	4.07	< 0.01*
4 hr.	99.85	14.893	87.55	12.223	90.50	14.752	100.70	18.823	3.71	0.015*
6 hr.	99.35	14.826	86.50	13.300	91.60	16.566	99.70	22.370	2.8	0.046*
12 hr.	100.20	16.008	86.00	14.513	91.80	17.893	98.50	22.630	2.62	0.057

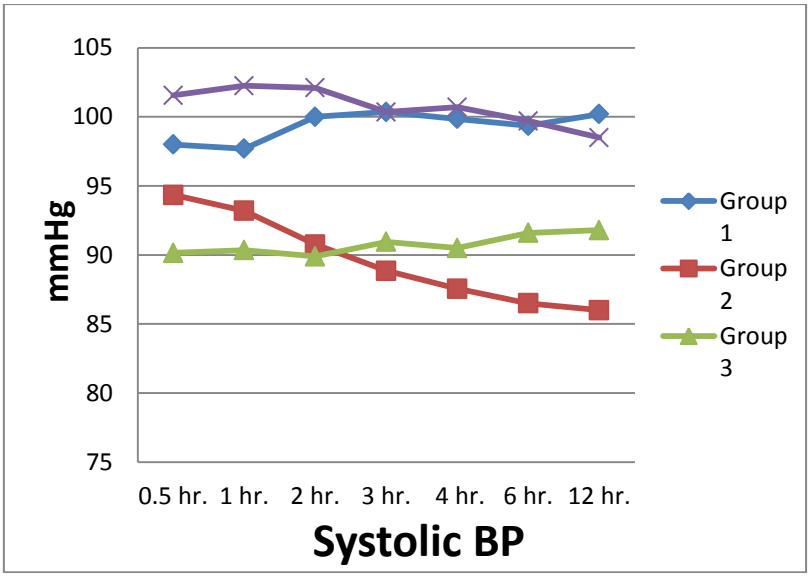


Fig. 19. *Comparing the studied groups regarding SBP over the postoperative follow up*

The diastolic blood pressure(DBP) (Table 10):

As regards the DBP after 30 min. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(63.05 ± 6.7mmHg) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 4** (**CC**) follow **Group 1** with mean (56.4 ± 4.27mmHg) which is highly significant difference(P<0.001) compared with the other two groups **Group 3 and Group 2.**
- **Group 3** (**CF**) **and Group 2** (**CD**) have the lowest values with means(54.2 ± 5.4 & 54.05 ± 5.31 mmHg) respectively which are statistically highly significant difference(P<0.001).

As regards the DBP after 1 hr. postoperatively:

The same interpretation as in 30 min. postoperative observation.

As regards the DBP after 2 hrs. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(65.15 ± 8.8mmHg) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**

- **Group 3** (**CF**) **and Group 4** (**CC**) follow **Group 1** with means (53.5 ± 7.23 &55.85 ± 4.94 mmHg) which are highly significant difference(P<0.001) compared with the other group **Group 2.**
- **Group 2** (**CD**) has the lowest value with mean (50.65 ± 5.63 mmHg) which statistically highly significant difference(P<0.001).

As regards the DBP after 3, 4, 6 and 12 hrs. postoperatively:

The same interpretation as in 2 hrs. postoperative observation.

Tab.10.Comparing the studied groups regarding DBP over the postoperative follow up

DBP over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
0.5 hr.	63.05	6.700	54.20	5.395	54.05	5.306	56.40	4.272	11.8	<0.001*
1 hr.	64.15	7.706	53.15	5.314	53.70	5.202	56.55	3.940	15.8	<0.001*
2 hr.	65.15	8.797	50.65	5.631	53.50	7.229	55.85	4.944	16.9	<0.001*
3 hr.	65.55	9.264	48.85	5.976	52.10	8.497	54.75	7.649	16.6	<0.001*
4 hr.	65.15	9.565	47.70	6.522	51.70	8.694	54.00	9.425	15.0	<0.001*
6 hr.	64.30	9.787	46.60	7.802	51.75	9.238	52.65	10.653	12.6	<0.001*
12 hr.	64.65	10.499	47.10	8.315	52.50	10.267	51.75	10.396	11.4	<0.001*

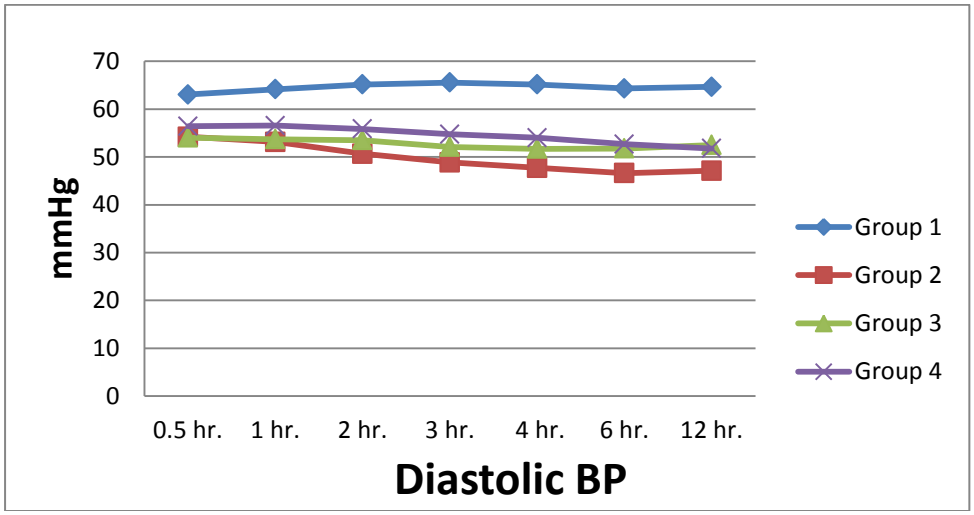


Fig. 20. *Comparing the studied groups regarding DBP over the postoperative follow up*

The oxygen saturation(SPO2) (Table 11):

As regards the SPO2 after 30 min. postoperatively:

Group 1 (**CB**), **Group 2** (**CD**) **and Group 4** (**CC**) have the highest values with means(98.55 ± 0.69 , 98.5 ± 0.76 & 98.85 ± 0.37 %) which is highly significant difference(P<0.001) compared with the other group **Group 3**(**CF**) which has the lowest value with mean (97.6 ± 0.88 %)**.**

As regards the SPO2 after 1, 2, 3, 4, 6 and 12 hrs. postoperatively:

The same interpretation as in 30 min. postoperative observation.

Tab.11. Comparing the studied groups regarding SPO_2over the postoperative follow up

SPO_2over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
0.5 hr.	98.55	0.686	98.50	0.760	97.60	0.882	98.85	0.366	11.8	<0.001*
1 hr.	97.70	0.656	97.90	0.552	96.35	1.089	97.25	0.223	24.6	<0.001*
2 hr.	97.35	0.875	97.70	0.470	95.55	1.234	97.80	0.410	32.9	<0.001*
3 hr.	97.40	0.502	97.60	0.502	95.80	1.281	97.50	0.512	24.2	<0.001*
4 hr.	97.20	0.695	97.15	0.489	95.20	1.361	97.30	0.470	29.2	<0.001*
6 hr.	97.40	0.502	97.30	0.571	95.20	1.005	97.30	0.470	50.4	<0.001*
12 hr.	97.40	0.598	97.15	0.587	95.40	0.753	97.10	0.447	45.8	<0.001*

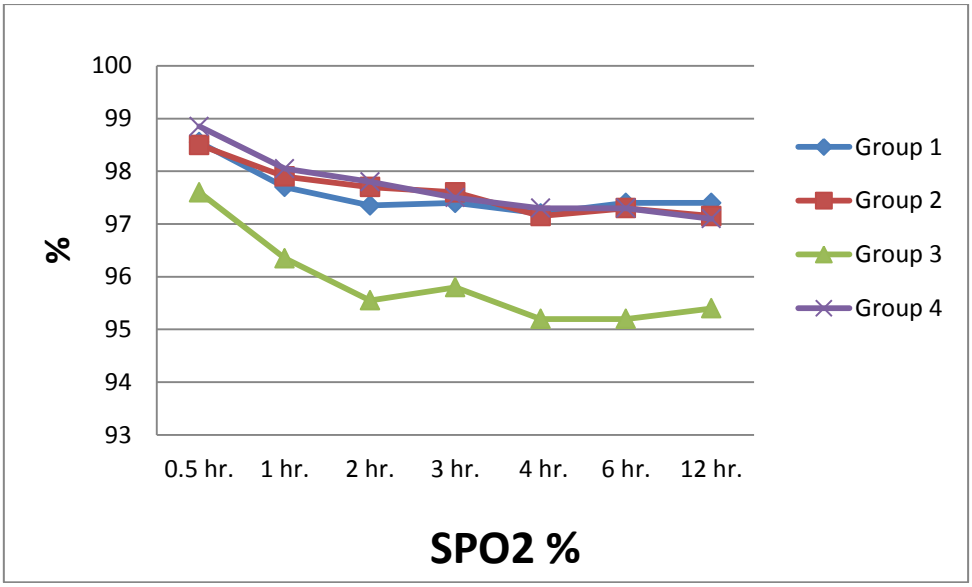


Fig. 21. *Comparing the studied groups regarding SPO_2over the postoperative follow up*

The repiratory rate(RR) (Table 12):

As regards the respiratory rate after 30 min. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(27.35 ± 4.07 br/m) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 2** (**CD**) and **Group 4** (**CC**) follow **Group 1** with means(25.05 ± 3.03 & 23.05 ± 3.12 br/m) respectively which are highly significant difference(P<0.001) compared with **Group 3.**
- **Group 3**(**CF**) has the lowest value with mean (19.95 ± 2.58 br/m) which is statistically highly significant difference(P<0.001).

As regards the respiratory rate after 1, 2, 3, 4, 6 and 12 hrs. postoperatively:

The same interpretation as in 30 min. postoperative observation.

Tab. 12. Comparing the studied groups regarding RR over the postoperative follow up

RR over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
0.5 hr.	27.35	4.068	25.05	3.034	19.95	2.584	23.05	3.119	18.7	<0.001*
1 hr.	28.15	3.645	25.45	4.032	19.80	2.504	23.00	3.145	22.1	<0.001*
2 hr.	28.15	3.660	24.00	2.865	19.90	2.653	23.40	3.470	22.5	<0.001*
3 hr.	27.75	3.985	23.45	3.284	20.10	3.160	23.35	4.029	14.9	<0.001*
4 hr.	28.25	4.766	22.85	4.475	20.10	3.945	23.15	4.614	11.6	<0.001*
6 hr.	28.20	5.708	23.10	5.097	19.90	4.919	23.70	5.948	8.4	<0.001*
12 hr.	28.30	6.283	22.05	5.462	19.40	4.914	23.70	6.665	8.7	<0.001*

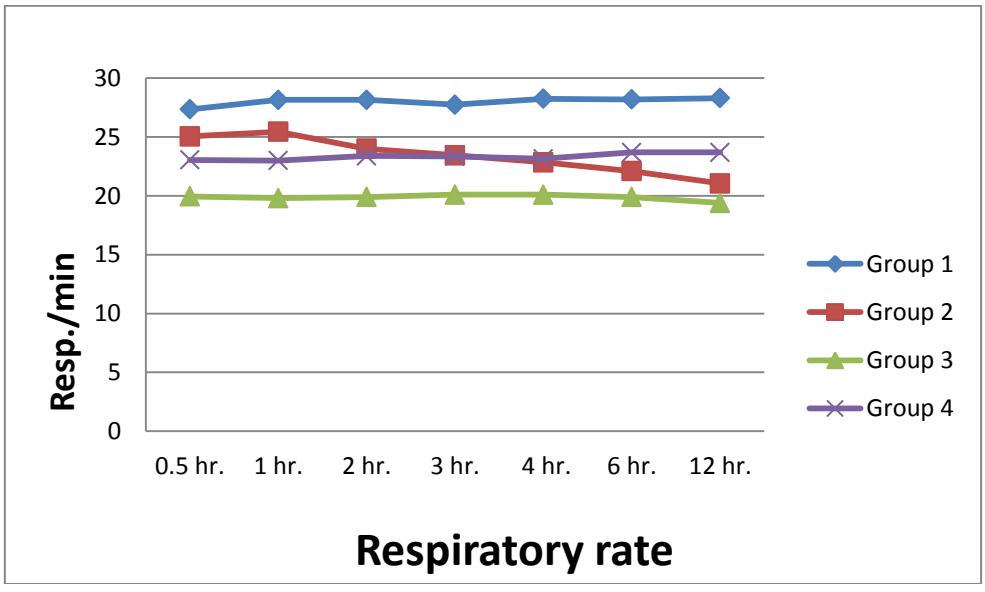


Fig 22. *Comparing the studied groups regarding RR over the postoperative follow up*

The pain score(FLACC) (Table 13):

Pain start at score ≥ 3

As regards the pain score after 30 min. and 1 hr. postoperatively: there were no statistical significant difference among the four groups.

As regards the pain score after 2 hrs. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(4.55 ± **1**) which is significantly different (P= 0.013) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 4** (**CC**) follow **Group 1** with mean (4 ± 0.97) which is significantly different (P= 0.013) compared with **Group 3** and **Group 2.**
- **Group 2** (**CD**) and **Group 3**(**CF**) have the lowest values with means (3.6 ± 0.68 & 3.85 ± 0.99) which are significantly different (P= 0.013).

As regards the pain score after 3 hrs. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(4.65 ± 0.99) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 3**(**CF**) and **Group 4** (**CC**) follow **Group 1** with means(3.7 ± 1.03 & 3.95 ± 1.43) respectively which are highly significant difference(P<0.001) compared with **Group2.**
- **Group 2** (**CD**) has the lowest value with mean (3.2 ± 0.833) which is statistically highly significant difference (P<0.001).

As regards the pain score after 4 hrs. postoperatively:

- **Group 1** (**CB**) it has the highest value with mean(5.05 ± 1.47) which is highly significant difference(P<0.001) compared with the other three groups **Group 2, Group 3 and Group 4.**
- **Group 3**(**CF**) follow **Group 1** with mean (4.15 ±1.39) which is highly significant difference(P<0.001) compared with **Group2 and Group 4.**
- **Group 4** (**CC**) follow **Group 3** with means(3.85 ± 1.89) which is highly significant difference(P<0.001) compared with **Group2.**
- **Group 2** (**CD**) has the lowest value with mean (2.8 ± 1.2) which is statistically highly significant difference (P<0.001).

As regards the pain score after 6 and 12 hrs. postoperatively:

The same interpretation as in 4 hrs. postoperative observation.

Tab. 13. Comparing the studied groups regarding pain score over the postoperative follow up

Pain score over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
0.5 hr.	4.20	0.767	4.35	0.670	4.05	0.887	4.15	0.875	0.48	0.69
1 hr.	4.25	0.716	3.85	0.587	3.80	0.695	4.10	0.788	1.83	0.14
2 hr.	4.55	0.998	3.60	0.680	3.85	0.988	4.00	0.973	3.8	0.013*
3 hr.	4.65	0.988	3.20	0.833	3.70	1.031	3.95	1.431	6.1	<0.001*
4 hr.	5.05	1.468	2.80	1.196	4.15	1.386	3.85	1.891	7.6	<0.001*
6 hr.	5.35	1.694	2.50	1.638	4.34	1.731	3.85	2.158	8.4	<0.001*
12 hr.	5.50	2.039	2.15	1.843	4.57	1.877	3.82	2.523	8.7	<0.001*

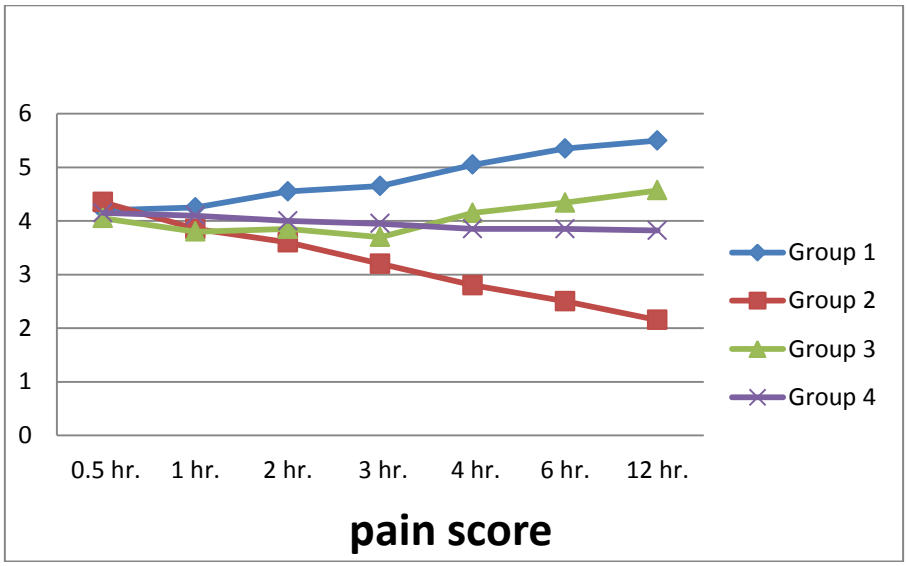


Fig 23. *Comparing the studied groups regarding pain score over the postoperative follow up*

The sedation scale (Modified Ramsay scale)(Table 14):

A score of 2 to 3 is anxiolysis, 4 to 5 is moderate sedation, 6 is deep sedation

As regards the sedation scale after 30 min. postoperatively:

- **Group 3**(**CF**) it has the highest value with mean(3.3 ± 0.73) which is highly significant difference(P<0.001) compared with the other three groups **Group 1, Group 2 and Group 4.**
- **Group 4** (**CC**) and **Group 2** (**CD**) follow **Group 3** with means(2.95 ± 0.69 & 3 ± 0.732) respectively which are highly significant difference(P<0.001) compared with **Group1.**
- **Group 1** (**CB**) has the lowest value with mean (2.15 ± 0.67) which is statistically highly significant difference (P<0.001).

As regards the sedation scale after 1 and 2 hrs. postoperatively:

The same interpretation as in 30 min. postoperative observation.

As regards the sedation scale after 3 hrs. postoperatively:

- **Group 3**(**CF**) and **Group 2** (**CD**) have the highest values with means(2.31 ± 0.67 & 2.2 ± 0.41)respectively which are highly significant difference(P<0.001) compared with the other two groups **Group 1 and Group 4.**
- **Group 4** (**CC**) follow **Group 3 and Group 2** with means(1.7 ± 0.47) which is highly significant difference(P<0.001) compared with **Group1.**
- **Group 1** (**CB**) has the lowest value with mean (1.2 ± 0.41) which is statistically highly significant difference (P<0.001).

As regards the sedation scale after 4hrs. postoperatively:

- **Group 2** (**CD**) has the highest value with mean (2 ± 0.46) which is highly significant difference(P<0.001) compared with the other three groups **Group 1, Group 3 and Group 4.**
- **Group 3**(**CF**) and **Group 4** (**CC**) follow **Group 3 and Group 2** with means(1.9 ± 0.64 &1.65 ± 0.49) respectively which are highly significant difference(P<0.001) compared with **Group1.**
- **Group 1** (**CB**) has the lowest value with mean (1.15 ± 0.37) which is statistically highly significant difference (P<0.001).

As regards the sedation scale after 6 and 12 hrs. postoperatively:

The same interpretation as in 4 hrs. postoperative observation.

Tab. 14. Comparing the studied groups regarding sedation score over the postoperative follow up

Sedation score over the Post-operative period	Group 1 (N=20)		Group 2 (N=20)		Group 3 (N=20)		Group 4 (N=20)		ANOVA	p
	Mean	± SD	Mean	± SD	Mean	± SD	Mean	± SD		
0.5 hr.	2.15	0.670	3.00	0.732	3.30	0.732	2.95	0.686	14.8	<0.001*
1 hr.	1.95	0.686	2.80	0.695	3.10	0.737	2.65	0.489	10.8	<0.001*
2 hr.	1.45	0.510	2.35	0.489	2.60	0.753	2.15	0.587	13.8	<0.001*
3 hr.	1.20	0.410	2.20	0.410	2.31	0.671	1.70	0.470	20.6	<0.001*
4 hr.	1.15	0.366	2.00	0.458	1.90	0.640	1.65	0.489	11.6	<0.001*
6 hr.	1.00	0.000	1.90	0.447	1.70	0.571	1.60	0.502	15.4	<0.001*
12 hr.	1.00	0.000	1.75	0.444	1.55	0.510	1.55	0.510	11.6	<0.001*

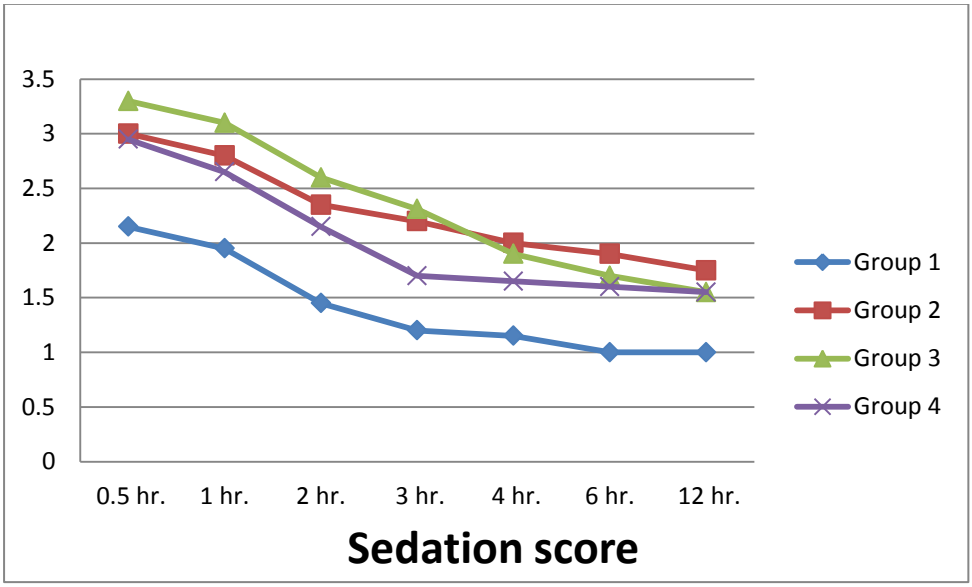


Fig. 24. *Comparing the studied groups regarding sedation score over the postoperative follow up*

The start of pain after the end of operation (score ≥3) (Table 15):

As regard time of start of pain (score ≥3) postoperatively after the end of operation:

- **Group 2 (CD)** has the highest value as pain start of delayed onset with mean of (12.2 ± 3.77 hrs) which is highly significant difference(P<0.001) compared with the other groups **Group 1, Group 3 and Group 4 (CC).**
- **Group 3 (CF) and Group 4 (CC)** follow **Group 2** with mean values of (9.50 ± 3.92 &9.35 ± 4.05 hrs) respectively which are highly significant difference (P<0.001) compared with **Group 1.**
- **Group 1 (CB)** has the lowest value as pain start earlier with mean (4.65 ± 3.24 hrs) which is statistically highly significant difference(P<0.001).

Tab. 15. Comparing the studied groups regarding start of pain after the end of operation.

Group	Start of pain		ANOVA	P
	Mean	± SD		
Group 1 (CB)	4.65	3.24	13.9	<0.001*
Group 2 (CD)	12.20	3.77		
Group 3 (CF)	9.50	3.92		
Group 4 (CC)	9.35	4.05		

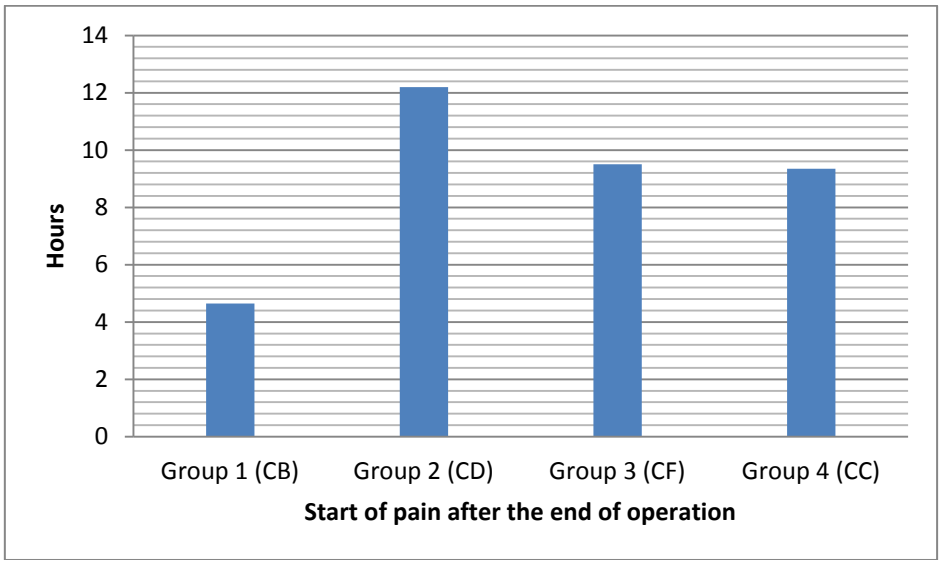


Fig. 25. *Comparing the studied groups regarding start of pain after the end of operation***.**

The total required doses of pethidine(Table 16):

As regard the total required dose of pethidine needed postoperatively:

- **Group 1 (CB)** has the highest value as patient needs larger doses of analgesics with mean of (25.15 ± 8.95 mg) which is highly significant difference(P<0.001) compared with the other groups **Group 2, Group 3 and Group 4.**
- **Group 3 (CF) and Group 4 (CC)** follow **Group 1** with mean values of (13.22 ± 7.1 &12.9 ± 9.24 mg) respectively which are highly significant difference (P<0.001) compared with **Group 2.**
- **Group 2 (CD)** has the lowest value as patient needs smaller doses of analgesics with mean (8.65 ± 6.49 mg) which is statistically highly significant difference(P<0.001).

Tab. 16. Comparing the studied groups regarding total required doses of pethidine

Group	Total required doses of pethedine		ANOVA	P
	Mean	± SD		
Group 1 (CB)	25.15	8.95	15.6	<0.001*
Group 2 (CD)	8.65	6.49		
Group 3 (CF)	13.22	7.10		
Group 4 (CC)	12.90	9.24		

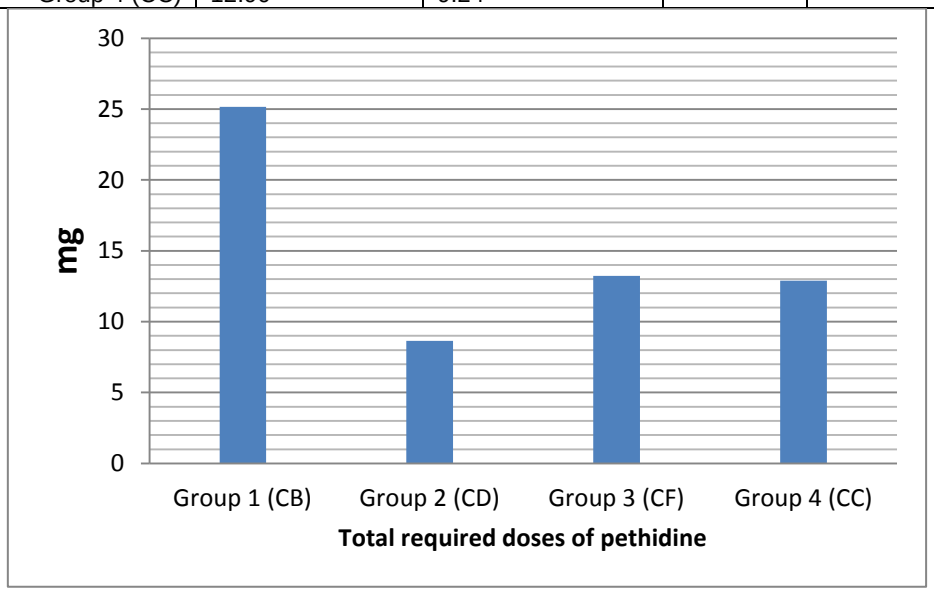


Fig. 26. *Comparing the studied groups regarding total required doses of pethidine*

The post operative complications (Table 17):

As the total number of the patients was 80 patients divided into four groups each consists of 20 patients the complications were minimal and in the form of vomiting and pruritis, and as regard the post operative complications there were no statistically significant difference among the studied groups.

Tab. 17. Comparing the studied groups regarding numbers and percentages of patients with postoperative complications.

Complications		Group				Total
		Group 1 (CB)	Group 2 (CD)	Group 3 (CF)	Group 4 (CC)	
vomiting	Count	3	1	2	1	7
	% within Group	15.0%	5.0%	10.0%	5.0%	8.8%
pruritis	Count	0	0	1	0	1
	% within Group	.0%	.0%	5.0%	.0%	1.2%

X^2=4.79 **P=0.57**

DISCUSSION

Caudal epidural analgesia is one of the most popular and commonly performed regional blocks in pediatric anesthesia. It is relatively easy to perform and provides efficient analgesia for both intraoperative and postoperative period. Although there are some studies which report caudal anaesthesia as the sole anaesthetic method in particular cases for infants and children, caudal anaesthesia is still combined with general anaesthesia for most of the cases***(Brenner et al., 2010)***.

The main disadvantage of caudal anesthesia is the short duration of action after a single injection of local anesthetic solution. Many drugs including epinephrine, morphine, clonidine, dexmedetomidine, ketamine, midazolam, and tramadol have been co-administered with caudal bupivacaine to maximize and extend the duration of analgesia. Caudal morphine extends postoperative analgesia, but it may be associated withdelayed respiratory depression. Caudal clonidine and midazolam have been associated with prolonged sedation. Behavioral side effects were reported with the use of the caudal ketamine, and an increased incidence of postoperative vomiting was observed with the use of caudal tramadol ***(Ansermino M et al., 2003).***

As regards the drugs used in this study, Bupivacaine has been in clinical use for more than 30 years. It is widely used for caudal epidural analgesia in children but it is associated with a number of side effects, including motor weakness, cardiovascular and central nervous system toxicity. In particular, there have been reports of death attributable to

bupivacaine - induced cardiotoxicity in adults after accidental intravenous injection. These cases and many unpublished instances of bupivacaine toxicity have resulted in the continuing search for new and safer local anesthetic agents ***(De Beer and Thomas, 2003).***

After caudal blockade in children, the administration of clonidine (1—5 mg/kg) as an adjunct to local anaesthetics has repeatedly been found to prolong and improve post-operative pain relief. The addition of clonidine (> 0.1 mg/kg/h) to a continuous epidural infusion of ropivacaine has also been found to improve the quality of post-operative pain relief in children. Kaabachi in 2002 and Rochette et al. in 2004 have suggested that intrathecal clonidine 2 mg/kg in a combination with bupivacaine is associated with extending the duration of postoperative analgesia with moderate side-effects ***(Rochette et al.,2004).***

On the other hand, recently dexmedetomidine has been investigated extensively in the pediatric population and there is now increasing evidence to support the use of this drug as sedative and anesthetic adjunct in children. The perioperative application of dexmedetomidine in children is discussed. However, although we have good clinical data in children, it is currently only approved by the US FDA for continuous infusion of up to 24 h in the adult intensive care unit. Hence, the uses of dexmedetomidine in children described in this review are 'off-label'***(Huupponen et al., 2008).***

The present study was conducted on 80 pediatric patients of both sexes 1 to 5 years old, with ASA physical status I, who were scheduled for variable elective sub-umbilical procedures. All patients received general anesthesia through laryngeal mask , after induction and before start of surgery caudal epidural blocks were performed for the patients. The patients were randomly divided into four groups: Group 1(CB) received caudal plain bupivacaine 0.125% 1ml/kg, group 2(CD) received caudal plain bupivacaine 0.125% 1ml/kg mixed with dexmedetomidine(2 µg/kg) , group 3(CF) received caudal plain bupivacaine 0.125% 1ml/kg mixed with fentanyl (2 µg/kg) and group 4(CC) received caudal plain bupivacaine 0.125% 1ml/kg mixed with clonidine(2 µg/kg) . All the 4 groups were comparable as regards age, sex, weight, type and duration of operation.

In our study As regards *duration of postoperative analgesia and start of pain,* group 2 (CD) has the highest value as pain start of delayed onset with mean of(12.2 ± 3.77 hrs)which is highly significant difference(P<0.001) compared with the other groups Group 1, Group 3 and Group 4.

Group 3 (CF) and Group 4 (CC) follow Group 2 with mean values of (9.50 ± 3.92 &9.35 ± 4.05 hrs) respectively which are highly significant difference (P<0.001) compared with Group 1.

Group 1 (CB) has the lowest value as pain start earlier with mean (4.65 ± 3.24 hrs) which is statistically highly significant difference(P<0.001).

This go with ***Anand et al., 2011*** In a randomised, prospective, parallel group, double-blinded study, 60 children were recruited and allocated into two groups: Group RD (*n*=30) received 0.25% ropivacaine 1 ml/kg with dexmedetomidine 2 µg/kg, making the volume to 0.5 ml and Group R

(*n*=30) received 0.25% ropivacaine 1 ml/kg + 0.5 ml normal saline. Induction of anaesthesia was achieved with 50% N2O and 8% sevoflurane in oxygen in spontaneous ventilation. An appropriate-sized LMA was then inserted and a caudal block performed in all patients. He found that The duration of postoperative analgesia recorded a median of 5.5 hours in Group R compared with 14.5 hours in Group RD, with a *P* value of <0.001. Group R patients achieved a statistically significant higher FLACC score compared with Group RD patients.

These results are in agreement with ***Mostafa*** e***t al 2008*** who studied 112 ASA I or II male and female children, aged 3–10yr, and their body weight between 10 –30kg, undergoing elective surgical procedures expected to last more than 90 min, and scheduled to receive general anesthesia combined with caudal extradural block were recruited. Anesthesia was induced with halothane and 60% nitrous oxide in oxygen and maintained with isoflurane (0.6 MAC corrected for age), using standard monitoring. Children were allocated randomly to one of five groups to receive a caudal injection: Group B received 1 ml/ kg of a mixture of equal parts of 0.25% bupivacaine, and 1% lidocaine; group D received the same mixture of local anesthetics plus dexmedetomidine 1.5µg/ kg; group C received the same mixture of local anesthetics plus clonidine 2µg/ kg; group T received the same mixture of local anesthetics plus tramadol 2mg/ kg; and group F received the same mixture of local anesthetics plus fentanyl 2µg/ kg. The duration of postoperative analgesia in Duration of analgesia was significantly longer in the four groups who received additives compared with control group:(245 ± 10) min in group B, (347 ± 13) min in group D, (350 ± 10) min in group C, (280 ± 20) min in group T, and (275 ± 15) min in group F (P < 0.05). In

groups D and C, the mean duration of analgesia was significantly longer than groups T and F ($P < 0.05$) .

Also these results go with the study These findings confirm previous studies ***Klimscha et al., 1998*** in which a mixture of 0.25% bupivacaine 1 mL/kg and clonidine 2 µg/kg produced a longer duration of caudal analgesia in children than bupivacaine alone (9.8 vs 5.2 hours) respectively.

Our study agree with ***El-Hennawy et al 2009*** who Study Sixty patients (6 months to 6 yr) were evenly and randomly assigned into three groups in a double-blinded manner. After sevoflurane in oxygen anaesthesia, each patient received a single caudal dose of bupivacaine 0.25% (1 ml kg^{-1}) combined with either dexmedetomidine 2 µg kg^{-1} in normal saline 1 ml, clonidine 2 µg kg^{-1} in normal saline 1 ml, or corresponding volume of normal saline according to group assignment. Addition of dexmedetomidine or clonidine to caudal bupivacaine significantly promoted analgesia time [median (95% confidence interval, CI): 16 (14–18) and 12 (3–21) h, respectively] than the use of bupivacaine alone [median (95% CI): 5 (4–6) h] with $P<0.001$.

Saadawy et al 2009 who studied Sixty children (ASA status I) aged 1–6 years undergoing unilateral inguinal hernia repair/orchidopexy were allocated randomly to two groups (n =30 each). Group B received a caudal injection of bupivacaine 2.5mg/ml, 1 ml/kg; Group BD received the same dose of bupivacaine mixed with DEX 1 µg/kg during sevoflurane anesthesia., he had found that The duration of analgesia was significantly longer ($P<0.001$) in Group BD compared with Group B ($P<0.01$). and this is in agree with our study.

As regard *the total required dose of pethidine* needed postoperatively: Group 1 (CB) has the highest value as patient needs larger doses of analgesics with mean of (25.15 ± 8.95 mg) which is highly significant difference($P<0.001$) compared with the other groups Group 2, Group 3 and Group 4.

Group 3 (CF) and Group 4 (CC) follow Group 1 with mean values of (13.22 ± 7.1 &12.9 ± 9.24 mg) respectively which are highly significant difference ($P<0.001$) compared with Group 2.

Group 2 (CD) has the lowest value as patient needs smaller doses of analgesics with mean (8.65 ± 6.49 mg) which is statistically highly significant difference($P<0.001$).

Manickam *et al 2012* studied Sixty children in the age group of 1–6 years undergoing subumbilical surgeries were included in the study. Group A received 1 ml/kg of 0.1% ropivacaine, group B received 1 ml/kg of 0.1% ropivacaine with clonidine 1 mcg/ kg, and group C received 1 ml/kg of 0.2% ropivacaine.. He found that The mean duration of analgesia was 243.7 ± 99.29 min in group A, 590.25 ± 83.93 min in group B, and 388.25 ± 82.35 min in group C. The duration of analgesia was significantly prolonged in group B compared to groups A and C with the P value of 0.001. At 8 h, all the 20 children in group A had received the first rescue analgesic compared to 18 children in group C and 3 children in group B.

Motschb et al.,1997 After induction of general anaesthesia caudal block was performed either with 1 ml . kg^{-1} bupivacaine 0.175% with the addition of clonidine 5 µg. kg^{-1} (n=20), or with 1 ml . kg^{-1} bupivacaine 0.175%

(n=20). The intraoperative anaesthetic requirements, the perioperative haemodynamic effects, respiratory rate, sedation score, postoperative pain scores and side effects were assessed by a blinded observer. A patient-controlled analgesia system was used for postoperative pain relief. The quality of postoperative pain relief was assessed using Smiley's pain analogue scale. Postoperative analgesia was significantly better in the clonidine group as evidenced by the total number of requests **(3** vs 12, P<0.05) and the total amount of tramadol (20.5 mg vs 72.8 mg, P<0.05) administered.

As regard *sedation levels* group 1 range (1-3) , group 2 range (1-3), group3 rang(1-5) and group 4 range(1-4), which are statistically highly significant difference among the follow up period (P<0.001) . This is in agreement with ***Lak et al., 2011***, in this clinical trial, 40 children aged 1-8 years who were candidates for elective inguinal hernia repair were studied. Induction and maintenance of anesthesia were achieved using sodium thiopenthal, halothane and nitrous oxide. Children were randomly divided into 2 groups in a double-blind fashion, and were given caudal anesthesia with 0.125% bupivacaine (1ml/kg) alone or b bupivacaine plus 2 μg/kg clonidine. Blood pressure and heart rate were recorded peri-operatively. Analgesia was evaluated using objective pain scale (OPS) and sedation was assessed using Ramsay sedation scale (RSS). Acetaminophen was administered rectally for cases with OPS score greater than five. He found that The mean score of sedation from the time of entering the recovery room till the time of receiving analgesic was 2.52 in group B and 3.09 in group BC. This difference was statistically significant (P = 0.002).

Sharpe et al., 2001 After obtaining written informed consent from parents and local ethics committee approval, we recruited 75 boys, ASA I or II, who were undergoing elective circumcision as a day case procedure anaesthesia was induced using sevofurane or halothane in nitrous oxide and 30% oxygen. Following induction of anaesthesia and venous cannulation, anaesthesia was maintained using spontaneous ventilation via a facemask delivering 1-2% halothane in 70% nitrous oxide in oxygen. Children were randomized, using a sealed envelope technique, to one of three treatment groups before caudal block was performed. The randomization was stratified in blocks of 12 to ensure equal distribution of the groups over time. Group C1 received 1.25 $mg.kg^{-1}$ (0.5 $ml.kg^{-1}$ of 0.25% solution) of bupivacaine plus 1 $\mu g.kg^{-1}$ clonidine. Group C2 received 1.25 $mg.kg^{-1}$ of bupivacaineplus 2 $\mu g.kg^{-1}$ clonidine. Group B received 1.25 $mg.kg^{-1}$ of bupivacaine only. He found in this study, arousal time, defined by time to first spontaneous eye opening, was significantly increased by clonidine in a caudal dose of 2 $\mu g.kg^{-1}$.

Lee and Rubin,1994 and ***Ivani et al., 1996*** in two independent studies, using clonidine in a dose of 2 $\mu g.kg^{-1}$, have shown increased postoperative sedation. ***Motsch et al., 1997*** Sedation was also increased in a study using 5 $\mu g.kg^{-1}$ of clonidine in subumbilical surgery.

As regard *Postoperative adverse effects* in our study none of the children had Hypotension, bradycardia, urine retention or nausea. three patients (15%) in group 1, one patient (5%) in group2, two patients (10%) in group 3 and one patients(5%) group4 suffered from vomiting that required ondansetron and only 1patient(5%) in group 3 suffer from pruritis that need

diphenhydramine which was with no significance difference this go with ***Shukla et al., 2011*** In the present double blind study, 90 children of ASA-I-II aged 3-8 years scheduled for infraumblical surgical procedures were randomly allocated to two groups to receive either ropivacaine 0.25% 1 ml/kg + clonidine 2 µg/kg (group I) or ropivacaine 0.25% 1 ml/kg + fentanyl 1 µg/kg (group II). Caudal block was performed after the induction of general anesthesia. He found that the side effects such as respiratory depression, vomiting bradycardia were significantly less in group I than group II ($P < 0.05$) ensuing more patient comfort.

This agree with ***El-Hennawy et al., 2009.*** The incidence of pruritis, diphenhydramine requirements, number of PONV, and ondansetron requirements (P¼0.246, 0.765, 0.596, 0.812, and 0.788, respectively). Mean times to first micturition were 8.1, 7.6, and 8.3 h in Groups A, B and C, respectively. One child in Group C required catheterization and one child in

Group A and two in Group B complained of difficulty with micturition but did not require catheterization.

Our results also go with ***Saadawy et al., 2009***.The incidence of vomiting, time for first micturition and spontaneous leg movements were not significantly different among both groups. No child in the two groups had any sign of motor weakness. One child in group B required urinary catheterization.

CONCLUSION

In conclusion, caudal additives like dexmedetomidine, fentanyl and clonidine prolong the duration of post operative analgesia after pediatric lower abdominal surgeries but bupivacaine dexmedetomidine mixture produced the longest duration of postoperative analgesia than the others and were associated with some degree of postoperative sedation which was accepted as it had been of minimal degree and short duration.

SUMMARY

Caudal blockade can be a safe and effective analgesia technique in suppressing some elements of the hormonal stress response. Caudal block, in combination with light general anesthesia, may be useful in premature children, those with comorbidity, as well as those with specific medical diseases such as cardiac disease or muscular atrophy.

It is sometimes a necessary part of our work to inflict pain during procedures, immunizations, and other treatments. In the past, there was a relative lack of accountability for providing pain relief. The major focus now is on how to properly assess pain. Culture has changed as evidenced by the new Joint Commission on Accreditation of Healthcare Organizations (JCAHO) regulations. Pain is considered "the fifth vital sign" requiring caregivers to regularly assess and address pain.

Several methods of assessing childhood pain have been developed upon the behavioral, physiological, and subjective components of pain.

Study was designed to compare the efficacy of caudal bupivacaine, bupivacaine-dexmedetomidine, bupivacaine-fentanyl and bupivacaine-clonidine mixtures in the relief of postoperative pain in children.

The study was conducted on 80 pediatric patients of both sexes with ASA physical status I, subjected to elective lower abdominal surgeries, and their ages were ranging between 1-5 years.

All patients were generally anesthetized by oxygen and halothane delivered through laryngeal mask . After induction and before start of surgery, the patients had caudal epidural blocks performed and they were divided into four equal groups each composed of 20 patients, according to the type of caudally injected drug:

Group1(CB) caudal bupivacaine 1ml/kg(0.125%)(control group).

Group2(CD)caudal bupivacaine 1ml/kg(0.125%)+ dexmedetomidine(2 µg/kg).

Group3 (CF) caudal bupivacaine 1ml/kg(0.125%)+fentanyl (2 µg/kg).

Group4(CC) caudal bupivacaine1ml /kg(0.125%)+ clonidine(2 µg/kg).

Patients were monitored along the first 12 hours postoperatively to assess hemodynamic and respiratory changes as well as analgesia using FLACC SCORE ***(Merkel et al., 1997),*** measurement of sedation scale using modified Ramsay scale ***(Ramsay et al. 1974)***, time to the 1st analgesic request. (I.e. at which analgesia in the form of iv pethidine will be needed), post anesthetic side effects(nausea, vomiting, urinary retention, pruritus).

In the present study, we have observed that Addition of either dexmedetomidine, fentanyl or clonidine to caudal bupivacaine significantly prolonged its analgesic effect but bupivacaine-dexmedetomidine mixture had longer effect than others.

In patients receiving dexmedetomidine added to caudal bupivacaine, there was hemodynamic stability, pain scores showing no or minimal pain, minimal sedation levels and no major complications were noticed. This analgesic effect extends from 18 to 20 hours postoperatively even after the period of assessment during the study.

Caudal dexmedetomidine has also proved to be safe in the concentration used and proved to prolong the local anesthetic analgesic duration by a period that reached up to 20 hours postoperatively.

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الملخص العربى

إن الألم الذى يتسبب فيه إجراء العمليات الجراحية ليشكل خطورة بالغة على المريض وخصوصا فى الساعات الأولى بعد إجراء الجراحة.

ومما لا شك فيه أن الألم الذى يحدث للأطفال بعد الجراحة لا يؤثر عليهم فحسب بل ينعكس بشكل غير مباشر على الآباء مما إقتضى ضرورة إيجاد حل لعلاج ذلك الألم.

ولذلك كانت طريقة تسكين الألم عن طريق الحقن الذيلى (أو الذنبى) فوق الأم الجافية فى الأطفال تعتبر طريقة سهلة وآمنة وفعالة لتسكين الألم لدى الأطفال بعد العمليات الجراحية كما أنها الطريقة الأكثر شيوعا بالنسبة لطرق التخدير الجزئي .

لم يكن علاج وتسكين الألم متاحاً للأطفال على مدى عقود طويلة فى الماضي إلا نادراً وذلك لأنه كان هناك اعتقاد شائع بأن الأطفال لا يشعرون بالألم لعدم نضج جهازهم العصبي المسئول عن الإحساس بالألم ، ولقد ثبت خطأ هذا الاعتقاد حتى بالنسبة للأطفال المبتسرين ويمتد الجزء المسئول عن الإحساس بالألم من الناحية التشريحية والفسيولوجية من المستقبلات الحسية للألم الموجودة بالجلد وحتى المنطقة الحسية الموجودة بقشرة المخ .

إن التسكين الذنبى للألم عند الأطفال يعتبر الطريقة المثلي لتسكين الألم بعد عمليات أسفل البطن الجراحية وهذه الطريقة تعتبر سهلة التنفيذ ولها مضاعفات يمكن تجنبها .

ولما كان تقييم وتحديد نسبة وجود آلام بالأطفال بعد الجراحة أمر صعب فقد قام العلماء بوضع مقاييس ومعايير لتحديد ذلك بدقة.

وبثبوت وجود آلام بالأطفال بعد الجراحة كان من الضرورى علاجه وذلك ماقد تم تناوله من خلال استخدام طرق التخدير الموضعية وخاصة التخدير الذيلى.

وفى هذه الدراسة قمنا بتناول كلا من عقاقير الديكسميديتوميدين والفنتانيل والكلونيدين وذلك عن طريق حقنهم كمادة إضافية للمخدر الموضعى باستخدام التخدير الذيلى وذلك لتقوية وتطويل فترة القضاء على الألم وكذلك الإحتياج إلى مسكنات بعد الجراحة دون ترك أى أعراض جانبية وذلك أثناء العمليات الجراحية الصغرى للأطفال.

طريقة البحث:

ولقد تم تخدير جميع المرضى تخديراً كلياً باستخدام غاز الأوكسجين والمخدر الاستنشاقى الهالوثان وتوصيل هذه الغازات للمرضى عن طريق الماسك الحنجري وقبل بداية الجراحة وفى ظل استمرار التخدير الكلى للمريض تم إعطاء المريض العقاقير المطروحة للدراسة عن طريق الحقن الذيلى وتم تقسيم المرضى الى اربعة مجموعات متساوية:

مجموعة ١(٢٠مريض): تم حقنهم عن طريق الحقن الذيلى بعقار البيوبيفاكين ٠.١٢٥% ١ ملل / كجم.

مجموعة٢ (٢٠مريض): تم حقنهم عن طريق الحقن الذيلى بخليط من عقارى البيوبيفاكين ٠.١٢٥% ١ ملل/كجم والديكسيميدوتين ٢ ميكروجرام /كجم.

مجموعة٣ (٢٠مريض): تم حقنهم عن طريق الحقن الذيلى بخليط من عقارى البيوبيفاكين ٠.١٢٥% ١ ملل/كجم والفنتانيل ٢ ميكروجرام /كجم.

مجموعة٤ (٢٠مريض): تم حقنهم عن طريق الحقن الذيلى بخليط من عقارى البيوبيفاكين ٠.١٢٥% ١ ملل/كجم والكلونيدين ٢ ميكروجرام /كجم.

وقد تم ملاحظة المرضى فى أول ١٢ ساعة بعد الجراحة لتقييم تسكين الألم باستخدام مقياس (FLACC) لقياس الألم، ودرجة الوعى باستخدام معيار درجة الوعى، والتغيرات المصاحبة لذلك فى ديناميكية الدم وسرعة التنفس، كما تم ملاحظة أية آثار جانبية؛ إن وجدت؛ مثل حدوث حكة بالجلد، حدوث قىء أو إحتباس بولى.

نتيجة البحث:

لقد لوحظ فى هذه الدراسة أن عقار البيوبيفاكين إذا ما تم حقنه وحده عن طريق الحقن الذيلى فى الأطفال يحدث تأثيراً مسكناً للألم، ولقد لوحظ أن اضافة أى من الديكسيميدوتين أوالفنتانيل أو الكلونيدين للبيوبيفاكين ساعد على إطالة مفعوله المسكن كثيراً وكان لخليط البيوبيفاكين و الديكسيميدوتين تأثير أطول من خليط البيوبيفاكين والفنتانيل او خليط البيوبيفاكين و الكلونيدين أو من البيوبيفاكين منفردا، ولقد احتاجت مجموعة البيوبيفاكين منفردا عدداً من جرعات المسكن أكثر كثيراً من مجموعتا البيوبيفاكين مع الفينتانيل والبيوبيفاكين مع الكلونيدين. أما مجموعة البيوبيفاكين مع الديكسيميدوتين فاحتاجت اقل جرعات من المسكنات.

لقد لوحظ أيضا أن خليط البيوبيفاكين مع الديكسيميدوتين أو الكلونيدين ؛ كان مصحوباً بدرجة من التأثير على درجة الوعى، ولكنها كانت مقبولة لأنها كانت درجات بسيطة ومرضية، وبالتالى لم تحتسب عيباً فى مقابل التأثير المسكن.

والمحصلة النهائية هى أن خليط البيوبيفاكين مع الديكسيميدوتين الذى أعطي عن طريق الحقن الذيلى نتج عنه تسكين للألم بعد الجراحة لفترة أطول كثيراً من العقاقير الأخرى، وقد صوحب الخليط بدرجة من التأثير على درجة الوعى ولكنها كانت مقبولة لأنها كانت درجات بسيطة ومرضية.

إنه ليوصى باستخدام خليط البيوبيفاكين و الديكسيميدوتين عن طريق الحقن الذيلى لتسكين الألم بعد الجراحة فى الأطفال فى جراحات اليوم الواحد.

مقارنة بين فاعلية إضافة بعض العقاقير للتخدير الذيلى للأطفال لعلاج آلام ما بعد العمليات الجراحية

توطئة للحصول على درجة الدكتوراه
فى التخدير والعناية المركزة

مقدمة من

الطبيب/ محمود إبراهيم عبد الفتاح

ماجستير التخدير والعنايه المركزة كلية الطب- جامعة بنها

تحت إشراف

ا.د/ سعد إبراهيم سعد

أستاذ ورئيس قسم التخدير والعناية المركزة كلية الطب- جامعة بنها

ا.د/ رضا خليل كامل

أستاذ التخدير والعناية المركزة كلية الطب- جامعة بنها

ا.م.د/ إيهاب سعيد عبد العظيم

أستاذ مساعد التخدير والعناية المركزة كلية الطب- جامعة بنها

كليـــــة طـــــب بنهـــــا.

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