# DISCUSSION

Caudal epidural analgesia is one of the most popular and commonly performed regional blocks in pediatric anesthesia. It is a reliable and safe technique that can be used with general anesthesia for intraoperative and postoperative analgesia in patients undergoing abdominal and lower limb surgery ***(De Beer and Thomas, 2003).***

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, ketamine, midazolam, and tramadol have been co-administeredwith caudal bupivacaine to maximize and extend theduration of analgesia. Caudal morphine extends postoperativeanalgesia, but it may be associated withdelayed respiratory depression. Caudal clonidineand midazolam have been associated with prolonged sedation. Behavioral side effects were reportedwith 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 These cases and many unpublished instances of bupivacaine toxicity have resulted in the continuing search for new and safer local anesthetic agents ***(De Beer and Thomas, 2003).***

Ketamine has been chosen to be used in this work because there is considerable evidence implicating ketamine in the spinal inhibition of nociceptive transmission, and it is as a derivative of phencyclidine has a chemical structure similar to that of bupivacaine and therefore has local anesthetic effects. These local anesthetic effects are also caused by N- methyl D- aspartate receptors antagonism (NMDA receptors are in the substantia gelatinosa of the spinal cord), opioid µ receptor agonism and voltage-sensitive sodium channel interaction ***(Brau et al., 1997)***. Ketamine has the significant advantage in that inadvertent intravascular injection will not result in the cardiovascular or central nervous system side effects that are seen with local anesthetics, specifically bupivacaine ***(Ansermino M et al., 2003).***

On the other hand, The neuraxial administration of neostigmine is known to produce analgesia in animals, human volunteers and patients with acute postoperative and chronic pain***( Lauretti GR et al.1999)***Spinal delivery of the cholinesterase inhibitor neostigmine inhibits the breakdown of the endogenous spinal neurotransmitter acetylcholine which has been shown to produce analgesia ***( Liu SS et al,1999)*** Neuraxial administration of neostigmine increases the concentration of acetylcholine in cerebrospinal fluid and produces antinociception in animals which is blocked by the intrathecal administration of a muscarinic antagonist ***(Naguib M, Yaksh TL.1997)***. The analgesic effect is thought to be mediated via spinal muscarinic M1 receptors and supraspinal muscarinic M1 and M2 and nicotinic cholinergic receptors ***(Bouaziz Het al1995)***. Auto-radiographic studies have shown muscarinic binding in substantia gelatinosa and, to a lesser extent, in the laminae III and V of the dorsal grey matter of the spinal cord, coincident with opioids and adrenergic sites ***( Lauretti GR1999).***

The present study was conducted on 75 pediatric patients of both sexes 2 to 14 years old, with ASA physical status I or II, who were scheduled for variable elective sub-umbilical procedures. All patients received general anesthesia through endotracheal tube and at the end of surgery, while still under anesthesia, caudal epidural blocks were performed for the patients. The patients were randomly divided into three groups: Group I received caudal plain bupivacaine 0.25% 1ml/kg, group II received caudal plainbupivacaine 0.25% 1 ml/kg mixed with neostigmine 2 µg/kg and group III received caudal plain bupivacaine 0.25% 1 ml/kg mixed with ketamine 0.5 mg/kg. All the 3 groups were comparable as regards age, sex, weight and ASA physical status.

In this study As regards *duration of postoperative analgesia* group II (Bupivacaine neostigmine group) had the longest duration of analgesia with a mean of 17.8400 hours, with a statistically highly significant difference (P<0.001) compared with group I (Bupivacaine group) and group III (Bupivacaine Ketamine group).

Group I (Bupivacaine group) had the shortest duration of analgesia with a mean of 5.0280 hours with a statistically highly significant difference (P<0.001) compared with the other two groups.

Group III (Bupivacaine Ketamine group) follow GroupII with mean duration of analgesia 11.1920 hours with a statistically highly significant difference (P<0.001) compared with the other two groups. And this is in agreement with ***Rajesh Mahajan et al 2004*** who study 80 boys aged two to eight years scheduled for surgical repair of hypospadias were allocated randomly to one of four groups (n = 20 each) and received either only caudal 0.25% plain bupivacaine 0.5 mL/kg (Group I) or 0.25% plain bupivacaine 0.5 mL/kg with neostigmine (Groups II–IV) in doses of 2, 3 and 4 µg/kg respectively. The duration of postoperative analgesia in Group I (5.1 ± 2.3 hr) was significantly shorter than in the other three groups (II –16.6 ± 4.9 hr; III – 17.2 ± 5.5 hr; IV – 17.0 ± 5.8 hr;( P < 0.05). Total analgesic (paracetamol) consumption was significantly more in Group I (697.6 ± 240.7 mg) than in the groups receiving caudal neostigmine (II – 248.0 ± 178.4; III – 270.2 ± 180.8 and IV –230.6 ± 166.9 mg; P < 0.05). Groups II, III and IV were comparable with regards to duration of postoperative analgesia and total analgesic consumption (P > 0.05).

Also these results go with the study done by ***Lee and Sanders (2000)*** on ropivacaine and ketamine co administered caudally in children, and these results are also supported by ***Weber and Wulf (2003)*** who showed reduction of analgesic doses during the 1st 24 hours on adding ketamine to bupivacaine.

# And this study agree with *Somasundaran S and MadhuGarasia 2008* who

Study 100 paediatric patients of ASA Grade I and II, aged between 1 to 7 years undergoing infra-umbilical surgery, during the study period. Cases were selected on the basis of simple random sampling method and were randomly allocated into three groups as follows: Group B: (n=34) who receives 0.75 ml/kg of 0.25% Bupivacaine caudally Group BK: (n=33) who receives combination of Ketamine 0.5 mg/kg + 0.75 ml/kg of 0.25% Bupivacaine caudally ,Group BT: (n=33) who receives combination of Tramadol 2 mg/kg + 0.75ml/kg of 0.25% Bupivacaine caudally , The mean duration of action after addition of Ketamine and Tramadol to Bupivacaine by the caudal epidural route was 9.3 h (559.39 ± 27.15 minutes) and 7.9 h (478.48 ± 54.15 minutes) respectively as compared to caudal Bupivacaine 4.0 h (240.59 ±15.36 minutes). ***Dinesh Kaushal et al 2009*** who studied 90 children, aged 2-10 years of ASA class I or II of either sex were randomly allocated into three groups (n=30) to receive a caudal injection of either 0.25% bupivacaine 1ml/kg or with 2μg/kg or 5μg/kg neostigmine, he had found that Caudal administration of bupivacaine with the addition of neostigmine resulted in superior analgesia compared with the plain bupivacaine group. Recovery to first analgesic times was 6.05 ± 2.04 h, 11.5 ± 3.42 h and 16.86 ± 4.92 h, respectively in the plain bupivacaine, bupivacaine with 2µg neostigmine and bupivacaine with 5µg neostigmine groups (p<0.05) and this is in agree with our study.

As regards *receiving of analgesic doses in the 1st postoperative 24 hours* the results showed that 25patients (100%) in group II(Bupivacaine neostigmine group) had a pain free postoperative period i.e. OPS < 4 that lasted more than 12 hours during which they did not need supplementary analgesia, while 7 patients (28%) in group III((Bupivacaine ketamine group) had a pain free period of 12hours .Only 5 patient (20%) in group I ((Bupivacaine group) had a postoperative pain free period of 6 hours. Meanwhile, no patient (0%) in the three groups had a postoperative 24 hour period of analgesia.

***Kumar P et al 2005*** studied 80 boys, ASA physical status I, aged 5–10 yrs., scheduled to undergo elective unilateral inguinal herniotomy. The study design was randomized and double-blind: patients were randomly allocated to 1 of the 4 groups (n= 20) by using a random number table. Group bupivacaine (B) received caudal injection of 0.25% bupivacaine 1 mL/kg; in addition, Groups bupivacaine-midazolam (BM), bupivacaine-ketamine (BK), and bupivacaine-neostigmine (BN) received preservative free midazolam 50 µg/kg, preservative free racemic ketamine 0.5 mg/kg, and neostigmine (containing methylparaben and propylparaben preservatives) 2µg/kg, respectively. He found that Both the duration of absolute analgesia and the time tofirst analgesic was significantly prolonged in GroupBN (442± 31 min; 19.6 ±4.2 h), Group BM (376 ±24 min; 16.8 ±3.9 h), and Group BK (336±16 min;11.6 ± 4.4 h) compared with Group B (238 ± 22 min;7.6± 5.2 h) (P < 0.05). Groups BN and BM had a significantly longer time to first analgesic compared with Group BK (P < 0.5). However, there was no significant difference between Groups BN and BM (P >0.05), although the duration of pain relief was greater in Group BN compared with Group BM. ***Abdulatif M and El Sanabary 2002*** they studied 60 boys, ASA physical status I, aged 2–10 yrs. old, undergoing hypospadias repair surgery. Patients were allocated randomly into one of three equal groups (n= 20) by a computer generated randomization scheme. Children in Group 1 received a caudal injection of 0.25% bupivacaine 1 mL/kg. Patients in Group 2 received an identical local anesthetic dosage mixed with neostigmine 2 µg/ kg. Group 3 received caudal neostigmine 2µ g/kg diluted in 0.9 NaCl solution to a total volume of 1 mL/kg.they found that Recovery to first Analgesic times were 22.8 ± 2.9 h, 8.1 ± 5.9 h, and 5.2 ± 2.1 h, respectively.

In the bupivacaine/neostigmine, bupivacaine, and neostigmine groups (P < 0.001). In addition, the bupivacaine and neostigmine groups were received more doses of paracetamol than the bupivacaine/neostigmine group to maintain adequate analgesia in the first 24 h postoperative.

As regard *cortisol level and glucose level* in this study At 30 min; There was no significant difference in between the three groups (p>0.05) ,At 4 hours, at 6 hours, at 8 hours, at 12 hours, There was statistically significant difference between both groups ІI and ІІI with group І. And no statistical Difference between groups ІI and ІІI (p<0.001).At 24 hours; Again there was no significant difference in between the three groups (p>0.05).***DeBeer and Thomas (2003),***

# As regards *hemodynamic changes*, this study revealed no significant changes in heart rate or mean arterial blood pressure among patients in the three groups whether those who received solitary drugs (bupivacaine) or those who received mixtures of drugs (bupivacaine with neostigmine and bupivacaine with ketamine). These results coincide with the studies done by *Somasundrana S. and Madhu G (2008)* who Studied 100 paediatric patients of ASA Grade I and II, aged between 1 to 7 years undergoing infra-umbilical surgery, during the study period. Cases were randomly allocated into three groups as follows: Group B: (n=34) who receives 0.75 ml/kg of 0.25% Bupivacaine caudally Group BK: (n=33) who receives combination of Ketamine 0.5 mg/kg + 0.75 ml/kg of 0.25% Bupivacaine caudally, Group BT: (n=33) who receives combination of Tramadol 2 mg/kg + 0.75ml/kg of 0.25% Bupivacaine caudally regarding caudal bupivacaine-ketamine mixture. This study showed no significant hemodynamic changes all over the study period. And this goes with the results obtained by *Baris and his coworkers (2003)* regarding caudal bupivacaine midazolam mixture.

In the present study, postoperative caudal analgesia using bupivacaine, bupivacaine-neostigmine or bupivacaine- ketamine mixtures was not shown to depress the respiratory function as evidenced by normal oxygen saturation (not less than 95%) in all groups throughout the period of study. No respiratory depression was recorded in any of the groups (respiratory rate <12/min).

These results are consistent with many other studies. For example, the study done by ***Khalil S. and her colleagues(1999)*** in which caudally administered bupivacaine (0.25% 1 ml/kg) provided adequate postoperative analgesia without affecting respiratory rate or arterial oxygen saturation.

***Naguib and his colleagues (1991),*** and ***De Negri and his coworkers (2001,)*** supported our findings in relation to respiratory function regarding caudally administered ketamine or bupivacaine ketamine mixture respectively.

The current results are supported by studies done by ***Kumar et al, (2005)*** but on bupivacaine midazolam mixture caudally administered in children. As regard *Postoperative adverse effects* in this study none of the children had Hypotension, bradycardia or respiratory depression. Two patients (8%) in bupivacaine group, four patients (16%) in bupivacaine neostigmine group and two patients in bupivacaine ketamine group (8%) suffered from vomiting. By the 4th postoperative hour, no residual motor block could be detected in any of the patients. ***Abdulatif M and El Sanabary 2002*** they studied 60 boys, ASA physical status I, aged 2–10 yr old, undergoing Hypospadias repair surgery. Patients were allocated randomly into one of three equal groups (n= 20) by a computer generated randomization scheme. Children in Group 1 received a caudal injection of 0.25% bupivacaine 1 mL/kg. Patients in Group 2 received an identical local anesthetic dosage mixed with neostigmine 2 µg/ kg. Group 3 received caudal neostigmine 2µ g/kg diluted in 0.9 NaCl solution to a total volume of 1 mL/kg.they found that Vomiting occurred in the recovery room in 5 (25%), 2 (10%), and 6 (30%) patients in the caudal bupivacaine/neostigmine, bupivacaine, and neostigmine groups, respectively (P < 0.01). Postoperative vomiting was not severe or repeated and was effectively managed with a single dose of IV Ondensetron 0.1 mg/kg.

All children in the three study groups were able to stand unassisted at the sixth postoperative h. No child had a recorded respiratory rate of < 15 breathes/min or showed any significant changes in heart rate and blood pressure in the first 24 postoperative h. There were no Instances of postoperative sedation, hypotension, bradycardia, or pruritus.

***Dinesh Kaushal et al 2009*** who studied 90 children, aged 2-10 years of ASA class I or II of either sex were randomly allocated into three groups (n=30) to receive a caudal injection of either 0.25% bupivacaine 1ml/kg or with 2μg/kg or 5μg/kg neostigmine, he had found that no significant difference in post-operative sedation scores (data not shown). No difference was observed regarding urinary retention requiring catheterization among the three groups. Times to first standing were not measured but we did not observe significant motor block and all children moved their legs spontaneously when leaving the recovery room 6 hr after caudal injection.

Vomiting occurred in recovery room in 2 (6.7%), 5 (16.7%) and 10 (33.3%) patients in the caudal bupivacaine, bupivacaine 2µg neostigmine and bupivacaine 5µg neostigmine groups, respectively. This difference was statistically significant between plain bupivacaine and bupivacaine 5µg neostigmine group (p<0.05). Postoperative vomiting was not severe or repeated and was effectively managed with a single dose of I.V Ondensetron 0.1 mg/kg. Oral intake and discharge from hospital were not delayed. There were no instances of post-operative sedation, hypotension, bradycardia or pruritus, in any of the groups.

***Olubukola O et al,2007*** who studied 62 child aged 2-8 years were randomized into three groups; Group 1 (n=20) had caudal injection of plain 0.125% bupivacaine 1 ml/kg. Group 2 (n=22) received caudal ketamine 0.5mg/kg diluted with 0.9% saline using the same weight-related volumes. Group 3 (n=20) received a similar dose of ketamine mixed with 0.125% bupivacaine 1 ml/kg, he found that Vomiting in the PACU occurred in three

(15%) patients in group 1, two (9%) patients in group 2 and three (15%) patients in group 3 (p=0.94). The incidence of postoperative complications was not significantly different in the three groups.