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***Research Article***

# STUDIES ON BIOCHEMICAL PROFILES OF DOGS AFTER EPIDURAL KETAMINE ALONE AND IN COMBINATION WITH PENTAZOCINE OR MEPERIDINE

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**ABSTRACT: Fifteen clinically healthy mongrel dogs of either sex of about one year of age were randomly divided in to three groups containing five dogs in each. The ketamine hydrochloride was administered epidurally at lumbosacral space in group I, whereas pentazocine and meperidine hydrochloride were given epidurally in combination with ketamine hydrochloride in group II and III, respectively. AST, ALT, glucose and creatinine showed a significant variation within normal physiological limits; whereas, GGT, BUN and total protein did not showed a significant variation (P>0.05) at respective intervals of observation. It may be concluded that epidural administration of ketamine in combination of opioids are safe and did not produce deleterious effect on vital organs.**

**Key words:** Biochemical studies, Epidural, Ketamine, Meperidine, Pentazocine.

## INTRODUCTION

Epidurally administered Ketamine in many herbivorous animal species appears to produce more consistently positive results because of longer plasma half life and less systemic effect as compared to intravenous route in dogs. Ketamine is adjunct to opioids are safer in small doses (Subramanium *et al.*, 2004). Epidural administration of opioid drugs is a relatively new technique which is used to provide intra and post-operative analgesia (Jones, 2001). De Rossi *et al*. (2008) reported the epidural administration of meperidine and lidocaine in combination resulted in a longer duration of analgesia. Bhannaria *et al.* (2005) studied the biochemical effects of combination of pentazocine and centbucridine in variable concentration in dogs and observed significant change in serum protein, glucose and blood urea nitrogen. The present paper deals the biochemical changes after epidural administration of ketamine alone and in combinations with meperidine or pentazocine in dogs.

## MATERIALS AND METHODS

The present research work was conducted on 15 clinically healthy male / female mongrel

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dogs of about one year of age. They were randomly divided into three groups containing five dogs in each group. The dogs were maintained in iso-managemental condition in the indoor ward of Ranchi Veterinary College clinics. Hygienic condition was maintained in and around the kennel and same type of feed was offered to each animal. Fresh water was made available freely in the kennel. All the dogs were dewormed with broad spectrum anthelmintic 7 days prior to the start of experiment.The dogs were kept off fed for 12 hours and withheld of water for 6 hrs was done before the commencement of experiment. The work has been approved by Institutional Animal Ethical Committee (IAEC) with certificate no. 528/RVC/IAEC/111.

Ketamine hydrochloride (Ketajet$^{R}$- Sterkem Pharma Pvt. Ltd) @ 3mg/kg bwt was administered epidurally at lumbo-sacrcal space in group I, whereas pentazocine (Fortwin$^{R}$ - Ranbaxy Lab. Ltd) @0.3 mg/kg bwt and meperidine hydrochloride (Demerol$^{R}$- Raj Pharma, MGS Road, Patna-7) @1 mg/kg bwt were given epidurally in combination with ketamine hydrochloride in group II and III, respectively. To accomplish epidural block, an 18-gauge 3.5 cm hypodermic needle was inserted percutaneously at the prepared site into the epidural space to inject analgesic agents.

For harvesting serum, 4-5 ml of blood was collected in a clean and dry test tube without anticoagulant by dry syringe through siliconised catheter placed in radial vein or recurrent tarsal vein. The blood was allowed to clot within the test tube in a slanting position for nearly 30 minutes and then centrifuged for 20 minutes at 3500 rpm. The supernatant serum was collected in clean dry test tube by rubber bulb pipette. The separated serum was analyzed for different biochemical parameters *viz*. AST (IFCC method), ALT (IFCC method), serum alkaline phosphatase (King and king's method), GGT (IFCC method), serum glucose (GOD-POD method), creatinine (IFCC), serum urea nitrogen (GLD Urease method) and total serum protein (Biuret method) before and at 1 hr, 2hr, 4 hr and finally at 24 hr after epidural administration of analgesic agents by ERBA Auto-analyzer Erba Manheim chem.-5 plus V2 using standard ERBA diagnostic kits.

**Statistical analysis**

One way analysis of variance (ANOVA) and Duncan multiple range test (DMRT) were used to compare the means at different intervals with base values as per method described by Snedecor and Cochran (1994).

## RESULTS AND DISCUSSION

Hepatic metabolism converts drugs and other compounds into products that are more easily excreted and that usually have a lower pharmacologic activity than the potent compound. Aspartate aminotransferase (AST) activities have been observed more after treatment at initial interval in group II and III as compared to group I (Table 1). However, these changes were transient and remained within normal physiological limits. An increase in AST level might be associated with increased cell membrane permeability in response to haemo-dynamic changes induced by anesthetic agents. More AST activity in the opioid groups may be attributed to the fact that the opioids are exclusively metabolized in liver hence causes more changes at cellular level.

It was interesting to note that the alanine aminotransferase (ALT) level increased significantly ($P<0.05$) up to 4 hours of

**Table 1: Mean ± S.E. value of AST (IU/L),ALT ((IU/L) ALP, (IU/L) and GGT (IU/L) of different groups at different time intervals of observation.**

| Parameters | Group | Period of observation (hours) | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 4 | 24 |
| AST (SGOT) | I | 37.42±0.31$^{a}$ | 39.24±0.34$^{b}$ | 39.40±0.40$^{b}$ | 39.88±0.88$^{b}$ | 37.20±0.77$^{a}$ |
| | II | 37.42±0.26$^{a}$ | 40.50±1.08$^{b}$ | 40.60±0.98$^{b}$ | 41.02±0.62$^{b}$ | 37.88 ±0.78$^{a}$ |
| | III | 37.96±0.48$^{ab}$ | 40.38±0.83$^{b}$ | 40.40±1.08$^{b}$ | 40.42±1.20$^{b}$ | 37.50±0.34$^{a}$ |
| ALT (SGPT) | I | 45.40±0.79$^{a}$ | 48.96±1.02$^{b}$ | 49.28±0.85$^{b}$ | 49.68±0.79$^{b}$ | 47.28±0.82$^{ab}$ |
| | II | 44.98±0.32$^{a}$ | 48.24±0.85$^{b}$ | 48.30±1.07$^{b}$ | 49.04±1.27$^{b}$ | 47.66±0.87$^{ab}$ |
| | III | 46.08±0.50$^{a}$ | 49.96±0.76$^{b}$ | 50.00±0.59$^{b}$ | 50.08±0.86$^{b}$ | 47.94±1.09$^{ab}$ |
| ALP Alkaline phosphatase | I | 45.80±1.07 | 47.20±0.77 | 48.20 ±1.07 | 46.20±0.95 | 47.00 ±0.63 |
| | II | 46.60±0.98 | 48.20±1.28 | 48.40±1.03 | 46.80±0.97 | 46.20±0.73 |
| | III | 47.60±0.87 | 48.40±0.75 | 48.60±1.03 | 47.00±0.32 | 47.40±0.93 |
| GGT | I | 7.5±0.74$^{a}$ | 9.30±0.49$^{bc}$ | 9.70±0.37$^{c}$ | 10.00±0.32$^{c}$ | 8.10±0.33$^{ab}$ |
| | II | 6.80±0.46$^{a}$ | 9.10±0.33$^{b}$ | 9.40±0.75$^{b}$ | 9.80±0.49$^{b}$ | 7.20±0.25$^{a}$ |
| | III | 7.00±0.42$^{a}$ | 9.60±0.73$^{b}$ | 9.90±0.87$^{b}$ | 10.00±0.63$^{b}$ | 7.40±0.37$^{a}$ |

Values with same superscripts in a row (small letters) did not differ significantly (P>0.05).
Values did not differ significantly among groups (P>0.05).

observation in all the groups as compared to their base line value (Table 1). The maximum increase (50.08±0.86) in its level could be recorded at 4 hours post-epidural in group III. The ALT value gradually declined after 4 hours of observation and reached to a level of non-significance by 24 hours post treatment. Non-significant change among groups at corresponding interval of observation was a consistent feature. AST and ALT activities is very sensitive to so many factors such as anesthesia (Kumar and Thurman 1978), hypoxia, stress due to anesthesia and surgery (Bain 2003), cardiac, skeletal and hepatic cell damage (Harper 1971) and other haemo-dynamic changes due to metabolism of anesthetics and toxins. An increase in AST and ALT levels have also been reported after epidural administration of buprenorphine and ketamine (Sharma and Pandey 2008).

There was non- significant increase (P>0.05) in the value of alkaline phosphates (ALP) in all the groups at different intervals of observation as compared to their base value (Table.1). Contrary to this, a significant increase in alkaline phosphate activity after epidural ketamine and buprenorphine in dogs have been reported by Sharma and Pandey (2008). Alkaline phosphatase is found in liver cells and it is associated with osteoblastic activity in bone. Liver ALP contributes to plasma ALP activity throughout the life and once the bone growth has reached the state of adult life, the liver becomes the primary source of plasma

**Table 2: Mean ± S.E. value of glucose (mg/dl), creatinine (mg/dl), BUN (mg/dl) and total protein (mg/dl) of different groups at different time intervals of observation.**

| Parameters | Group | Period of observation (hours) | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 4 | 24 |
| Glucose | I | 75.80±1.51$^{a}$ | 80.20±0.18$^{bc}$ | 82.40±1.00$^{c}$ | 80.40±0.67$^{c}$ | 77.20±0.72$^{ab}$ |
| | II | 72.60±1.51$^{a}$ | 78.52 ±1.79$^{b}$ | 78.62±2.04$^{b}$ | 79.20±1.25$^{b}$ | 74.82±0.93$^{ab}$ |
| | III | 73.92±1.67$^{a}$ | 78.56±0.48$^{bc}$ | 79.00±1.85$^{c}$ | 79.20±0.52$^{c}$ | 74.48±0.99$^{ab}$ |
| Creatinine | I | 0.64±0.14$^{a}$ | 0.80±0.16$^{ab}$ | 0.75±0.17$^{ab}$ | 0.98±0.20$^{ab}$ | 1.14±0.15$^{b}$ |
| | II | 0.61±0.05$^{a}$ | 0.68±0.09$^{ab}$ | 0.67±0.04$^{ab}$ | 1.00±0.16$^{b}$ | 0.98±0.21$^{b}$ |
| | III | 0.67±0.07$^{a}$ | 0.73±0.10$^{ab}$ | 0.75±0.18$^{ab}$ | 1.05±0.05$^{b}$ | 1.02±0.14$^{b}$ |
| Blood Urea Nitrogen (BUN) | I | 11.80±0.58$^{ab}$ | 12.40±0.51$^{ab}$ | 11.40±0.51$^{a}$ | 12.90±0.23$^{b}$ | 13.01±0.25$^{b}$ |
| | II | 11.60±0.40$^{a}$ | 11.40±0.40$^{a}$ | 11.40±0.60$^{a}$ | 13.00±0.32$^{b}$ | 12.80±0.20$^{b}$ |
| | III | 11.40±0.24$^{a}$ | 11.60±0.51$^{a}$ | 11.60±0.24$^{ac}$ | 12.60±0.40$^{bc}$ | 12.80±0.20$^{b}$ |
| Total protein | I | 6.65±0.16 | 6.92±0.21 | 7.06±0.14 | 6.68±0.09 | 6.74±0.21 |
| | II | 6.72±0.20 | 6.94±0.17 | 7.10±0.20 | 7.19±0.21 | 7.20±0.10 |
| | III | 7.00±0.36 | 7.14±1.07 | 7.17±0.22 | 7.19±0.15 | 7.23±0.19 |

Values with same superscripts in a row (small letters) did not differ significantly (P>0.05).
Values did not differ significantly among groups (P>0.05).

ALP. In normal liver, bile duct epithelium has most of ALP activity (Kaneko 1989).

The importance of gamma–glutamyl transferase (GGT) activities in liver dysfunction has been emphasized in animals by various workers. CNS depressant anaesthetics causes some alterations in cell membrane permeability, which may permit these enzymes to leak from the cells. In the present study, a transient increase within physiological limits in GGT activities in all the groups (Table 1) could also be attributed to metabolic disturbances in liver (Baxter and Miert 1983) caused by altered blood flow to the liver.

Hyperglycemia appeared to be a consistent feature in all the groups following administration of different anesthetic regimen in the animals. A significant increase (P<0.05) in serum glucose level could be observed at hour 1, 2, and 4 post induction in group I, II and III as compared to their base line value (Table 1). The increase in serum glucose level, however, reached to a level of insignificance by 24 hours of observation. The anesthetic drugs used in different groups did not show any significant alteration in the level of serum glucose among the groups. This is in consonance with the findings of Singh *et al.* (2005). Chauhan and Pandey (2006) also observed increase in serum glucose level after epidural administration of fentanyl and ketamine in dogs. The increased level of blood glucose may be attributed to inhibition of insulin from beta cells of pancreas, increase in adreno-cortical hormones during

anesthesia and mobilization of liver glycogen under the influence of increased adrenaline level. Glucocorticoids liberated during stress are also considered to cause hyperglycemia in man (Lacoumenta *et al*., 1987).

A transient changes in creatinine and blood urea nitrogen (BUN) at different intervals could be recorded but the alteration remained within normal physiological limits in all the groups (Table 2).There was significant increase ($P < 0.05$) in serum creatinine level at 24 hrs intervals in group I, whereas groups II and III showed significantly higher level of creatinine and BUN at 4 hours interval. A progressive increase in the serum creatinine level was apparent in group I and III, whereas the animals of group II did not show a definite pattern of alteration. The increase in serum creatinine and BUN levels in all the groups may be attributed to anaesthetic effect of ketamine along with meperidine and pentazocine synergistically. Ketamine temporarily increases the renal blood flow causes stress and temporary damaging effect to kidney, which in turn might be responsible for transient increase in serum creatinine and BUN. Ketamine increases renal blood flow due to increase in mean arterial pressure, heart rate and cardiac output (Chu Lin, 2007).

Similar findings have also been reported after epidural administration of ketamine alone and in combination with buprenorphine in dogs (Sharma and Pandey, 2008). Bhannaria *et al.* (2000) also recorded increase level of BUN after epidural administration of centbucridine hydrochloride with xylazine and ketamine in dogs.

A more non- significant decrease at initial and later intervals in group II and III (Table 2) might be due to more stress after epidural administration of ketamine along with opioids. Stress may be responsible for more production of glucocorticoids in body, which may cause rapid mobilization of amino acid from storage tissue. Eventually, the protein sources are converted to carbohydrate for energy through glyconeogenesis (Sheldon *et al.*,1977), which might be reason for decrease in total protein. The decrease in protein level also suggested an influx of fluid into the vascular space (Bennet *et al.*, 2009).

## CONCLUSION

Epidural administration of ketamine in combination with pentazocine and meperidine produced transient and within physiological limits of variations in all the groups. In ketamine group, analgesia was noticed at 5 min. and progressed upto 30 min., whereas in pentazocine group and meperidine group, the analgesia persisted up to 60 min of observation. Evidence of analgesia was absent in all the groups by 120 min. of observation.The duration of analgesia, time of standing and recovery time were significantly longer in pentazocine group and meperidine group as compared to ketamine group. Hence these combinations of opioids along with ketamine as epidural anesthetic agent could be considered safe for achieving analgesia of hind quarters of dogs.

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