**EFFECT OF CONSTANT RATE INFUSION OF TRAMADOL-XYLAZINE AND PENTAZOCINE XYLAZINE ON ACUTE PAIN RESPONSE IN XYLAZINE-PENTOBARBITONE ANAESTHESIZED DOGS UNDERGOING DIGITAL AMPUTATION**

**ABSTRACT**

The study evaluated the effect of constant rate infusion of tramadol-xylazine and pentazocine-xylazine on pain in dogs undergoing digital amputation. Twelve mongrel used for the study were randomly assigned to four groups (n=3). Group 1 received loading dose (LD) Xylazine (1mg/kg IV) and Pentobarbitone sodium (Na) (30mg/kg IV) [LD-XP] prior to digital amputation (DA).Group 2 received LD-XP andXylazine (1mg/kg/hr) by constant rate infusion (CRI IV) prior to DA. Group 3 received LD Xylazine (1mg/kg IV), Pentobarbitone Na (30mg/kg IV), CRI Xylazine (1mg/kg/hr) and Tramadol (1mg/kg/hr) prior to DA. Group 4 received LD-XP, CRI Xylazine (1mg/kg/hr) and CRI Pentazocine (1mg/kg/hr) prior to DA. Results of the pain score evaluation showed that at 1, 3, 6 and 24 hours post-surgery (PS), group 4 had the lowest (p<0.05) pain score followed by group 3. Group 4 animals had a significantly (p<0.05) higher heart rate and pulse rate values at 3 and 120 hours. The respiratory rate of group 4 was significantly higher (p<0.05) when compared with the other groups at 3 and 24 hours. It was concluded that CRI pentazocine-xylazine provided better analgesia in the dog DA model.

**KEYWORDS;** pain, tramadol, analgesia, multi-modal, pentazocine, xylazine

**INTRODUCTION**

Acute pain refers to pain that lasts a few hour or days and does not outlast the healing process (Molony and Kent, 1997). It warns the animal of the potential for injury, therefore, a host of protective reflexes such as withdrawal of a damaged limb, muscle spasm and autonomic responses are often seen in cases of acute pain (Bowdle, 1998). Acute pain is usually nociceptive, but may be neuropathic (Brogden et al., 1973). It can be transient in nature such as pain associated with needle prick (eg. drug injection and venipuncture) or experimentally applied noxious stimulus that does not produce noticeable tissue damage (Molony and Kent, 1997). Acute pain in animals can also be post-procedural or post-surgical pain which is associated with procedures or surgery (Molony and Kent, 1997). Procedures which resulted in acutely painful conditions thereby necessitating analgesic administration in dogs were limb amputation, limb-sparing bone cancer resection, thoracotomy, cervical instability repair and humeral fracture repair (Hansen and Hardie, 1993). Tissue injury is a consequence of the above mentioned procedures and thus pain resulting from these procedures were longer lasting than momentary pain (Booth and McDonald, 1982). According to the American Veterinary Medical Association Policy Statement and Guidelines (AVMAPSG, 1999), pain is a clinically important condition that affects an animal's quality of life negatively. Therefore husbandry practices, drugs and techniques used to prevent and control pain must be well suited for individual animals, procedure to be performed and degree of pain (Short, 1999). Pain management programs involve use of analgesic techniques peri-operatively to decrease somatic as well as autonomic reflex responses to nociceptive stimuli, reduce stress and ensure comfort (Kehlet and Dahl, 2003). Thus bearing these pain management objectives in mind, various protocols of multimodal analgesia or balanced anaesthesia have been proved effective in establishing adequate analgesia in dogs undergoing ovariohysterectomy (Kongara et al., 2011) and orchiectomy (Zeiler et al., 2014).

Multimodal or balanced analgesia is achieved when drugs with different modes of action or that act on different receptor sites are combined to provide good analgesia (Matthews and Carroll, 2007). It had been suggested that use of more agents at smaller doses maximized desired analgesic effects while minimizing side effects of agents combined (Brown et al., 2018) Previously, due to the analgesic efficacy of opioids, balanced analgesic regimens relied almost exclusively on opioids administered as intermittent boluses or as continuous infusions to manage

nociception intraoperatively and pain postoperatively (Brown et al., 2018). owever, to minimize oipCurrently, to minizi Ccc Currently to minimize opioid related adverse effects, opioid combinations are used notably opioid -non-steroidal anti-inflammatory drugs (Cannon et al., 2011), opioid-local anaesthetic-N-Methyl-D-Aspartate (NMDA) receptor agonist (Muir et al., 2003), opioid-benzodiazepine and opioid-alpha2 agonist (Lena et al., 2008). Depending on patient need, routes via which these drugs may be administerd include parenteral (IV, IM or SC), oral, intra-articular, transdermal or transmucosal (Matthews and Carroll, 2007).

Tramadol a centrally acting analgesic is a synthetic opioid, chemically trans-2 (dimethylaminomethyl)-1-(3-methoxyphenyl)-cyclohexanol hydrochloride that is available as oral or parenteral form (Upadhyay et al., 2006). It possesses weak affinity for the mu-opioid receptor and less affinity for the kappa and delta receptor (Grond and Sablotzki, 2004). It is an active analgesic used to relief moderate to moderately severe forms of acute or chronic pain (Barkin, 2008), orthopaedic pain (McCarberg and Tenzer, 2013), gynaecologic/obstetric pain (Peters *et al*., 1996), as well as pain in other organs (Leppert and Luczak, 2005). The opioid tramadol hydrochloride has an advantage over other opioids due to its dual mechanism of action and minimal side effects (Perez-Urizar et al., 2014). Due to its short duration of action, a combination with other classes of analgesics to produce multimodal analgesia had been suggested (Muir et al., 2003). A study conducted in dogs by Kongara et al. (2010) reported that pre-operative subcutaneous injection of tramadol and morphine provided an adequate degree of post –operative analgesia in dogs after ovariohysterectomy. However, better post-operative analgesia was achieved with a combination of morphine and tramadol. Also, as reported by Zeiler et al (2014) multimodal therapy using medetomidine-ketamine in combination with tramadol provided adequate anaesthesia and analgesia for orchiectomy in cats.

Pentazocine on the other hand is a benzomorphan which is chemically related to morphine consisting of a racemic mixture of dextro- (d) and laevo- (l) isomers which are soluble in acidic aqueous solutions (Henderson, 2008). The action of pentazocine is due to its l-isomer and it is a potent analgesic with both agonist action at OP2 (ƙ) receptors and antagonist action at OP3 (µ) opioid receptors (Henderson, 2008). When administered intravenously, its potency varied from one-third to one-quarter the potency of morphine (Henderson, 2008). In a study conducted to compare the analgesic effects of IV buprenorphine and pentazocine, the researchers concluded that both drugs may be used effectively to provide relief of severe pain post-surgery (Harmer et al., 1983). Also, Yadav and Gupta (2016), administered pentazocine (300 mcg) via epidural, intramuscular and slow bolus intravenous infusion to human patients that underwent upper abdominal surgery. The outcome of their study suggested that pentazocine produced adequate post-operative analgesia by all techniques used in the study. More so, in low risk paturients that underwent caesarean section under spinal anaesthesia, intramuscular injections of pentazocine-diclofenac for post caesarean section analgesia was more effective in achieving pain relief than pentazocine alone (Egede et al., 2017). Furthermore, continous intravenous infusion of pentazocine proved effective in management of trauma induced pain (Bion, 1984).

Xylazine hydrochloride a 2-(2,6 dimethylphenylamine)-4H-5, 5 dihydro-1,3 thiazine hydrochloride drug, α2adrenoceptor agonist is extensively used due to its potent sedative, analgesic and muscle relaxant properties in animals ( Green and Thurmon, 1988). Xylazine produces antinociceptive by activation of pre-synaptic α2 receptor, thus leading to decrease in the amount of noradrenaline and dopamine (Torneke et al., 2003; Curro et al., 2004). It had been demonstrated that α2-agonists such as xylazine have a significant hypnotic interaction with anaesthetic agents and an analgesic interaction with opioids (Taqa, 2012). Specifically, Taqa (2012) in a study undertaken to evaluate the antinociceptive interaction between tramadol and xylazine concluded that the administration of tramadol and xylazine markedly reduced the median effective dose (ED50) of both drugs for antinociceptive effect in mice. According to these authors the finding suggested a synergistic (super-additive) interaction between tramadol and xylazine. Also, combination of xylazine and pentazocine for neuroleptanalgesia was found suitable for majority of surgical interventions requiring sedation and analgesia in bovine (Aher, 2003). Bearing in mind the benefits of alpha2agonist -opioid interaction, it is therefore essential to conduct this study to assess the analgesic and possible adverse effects of administration of tramadol-xyalzine and pentazocine-xylazine to pentobarbitone anaesthesized dogs undergoing digital amputation. The findings of this study will provide new insight on the analgesic efficacy and possible adverse effects of this new multimodal analgesic regimen.

**METHODOLOGY**

**Ethical consent**

This study was approved by the Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, University of Nigeria, Nsukka (IACUC, FVM UNN) with the application reference number; FVM-UNN-IACUC-2019-1130.

**Animals and care**

This study was performed using twelve (12) adult mongrel with a mean weight of 5.95± 0.34 kg, housed for two weeks at the animal house of the Department of Veterinary Surgery, University of Nigeria Nsukka for acclimatization. During acclamatization, dogs were vaccinated with rabies, distemper, hepatitis, leptovirus, parvovirus and parainfluenza virus vaccines. They were also confirmed to be free from blood borne and gastrointestinal parasites using blood smear and faecal floatation tests. They were fed solely on commercial dog food (Mutt® Weba, USA) and water was provided *ad libitum* throughout the study period.

**Experimental design**

The dogs were randomly assigned to four (4) groups of three (n=3) animals each as shown below:

**Group 1**: Loading dose (LD) Xylazine (Xyl-M2®, Berendonk Drug Company, Belgium) (1mg/kg IV) + Pentobarbitone Na (Merfpento®, Alpha laboratories, Nigeria) (30mg/kg IV) + Normal saline infusion (Juhel®, Nigeria) (10ml/kg/hr) + Digital amputation (DA).

**Group2**: LD Xylazine (1mg/kg IV) + Pentobarbitone Na (30mg/kg IV) + CRI Xylazine (1mg/kg/hr IV) + DA.

**Group 3**: LD Xylazine (1mg/kg IV) + Pentobarbitone Na (30mg/kg IV) + CRI Xylazine (1mg/kg/hr IV) + CRI Tramadol (Pauco®, Pauco Pharmaceutical, India) (1mg/kg/hr IV) + DA.

**Group 4**: LD Xylazine (1mg/kg IV) + Pentobarbitone Na (30mg/kg IV) + CRI Xylazine (1mg/kg/hr IV) + CRI Pentazocine (Pentalab®, Laborate Pharmaceutical, India) (1mg/kg/hr IV) + DA.

**Induction of anaesthesia**

Prior to digital amputation in the respective groups, sedation was achieved using xylazine Hcl while anaesthesia was achieved using Pentobarbitone Na.

**Surgical procedure (digital amputation)**

Each dog was placed on left lateral recumbency and the skin around the fourth digit of the right hindlimb was properly shaved using a razor blade. The area was then disinfected using chlorhexidine based antiseptic (Purit). A 2cm skin incision was made just below the metatarso-phalangeal joint of the limb. The blood vessels were ligated using a size 2/0 chromic catgut. Using a blunt dissection, the phalanx was excised from the surrounding fascia and skin. Skin apposition was done using a simple interrupted suture pattern with silk 2/0. Post-operatively, the animals were injected with 20% oxytetracycline (20mg/kg, IM) to avoid secondary bacterial infection. Interventional analgesia was achieved using Diclofenac (1mg/kg IM) given from day 1 post surgery for 3 days.

**Data collection**

**Physiologic parameters:** The physiologic parameters (heart rate, pulse rate, respiratory rate, temperature and SPO2) were measured using a Veterinary patient monitor (TM-9009, Technocare Medisystems, India). These parameters were taken at baseline, intra operatively (immediately after the digit was removed), then postoperatively at 1, 3, 6, 24, 72 and 120 hours.

**Assessment of pain:** Pain assessment was done postoperatively at 1, 3, 6, 24, 48 and 72 hours. A video recording of the animal at rest and during movement was made to aid in this subjective assessment. Videos obtained were transferred to a laptop and video clips were viewed and pain scoring performed by a blinded scorer who was ignorant of treatments administered. The pain scoring was done using the Glasgow composite pain scale (modified). Specifically, numerical scores of 0 to 4 were assigned to different observed gaits as the dogs walked as shown below:

Normal gait = 0

Lame gait =1

Slow or reluctant gait = 2

Stiff gait =3

Hanging of limb/Limping = 4

**Biochemical analysis:** Three millilitres (3ml) of blood was collected from the cephalic vein at baseline (before injection of any drug) and post operatively at 24, 72 and 120 hours for biochemical analysis. Blood, was dispensed into plain sample bottles for serum biochemistry. Serum was obtained by the centrifugation of the blood at 3,000 rpm for 10 minutes. The serum alanine aminotransferase, aspartate aminotransferase, urea, total protein, bilirubin and creatinine levels of the dogs were assayed using Randox® kits under standard conditions.

**Data analysis**

The data analysis was performed using the IBM SPSS 20 software. The physiological and biochemical parameters of the various groups were compared using two way analysis of variance (ANOVA) to ascertain the differences between mean values obtained in the four groups and also time dependent changes in the studied parameters within each group. Post hoc test was done using Duncan multiple range test and mean values compared were considered significantly different at probability value less than 0.05. The pain scores were analysed using Kruskal-Wallis non-parametric test.

**RESULTS**

**Heart rate, pulse rate, respiratory rate and peripheral capillary oxygen saturation of the different groups**

The values presented in table 1 shows that the heart rate (HR) of the four groups decreased intra-operatively and at 1 hour post digital amputation though not significantly (p>0.05). At 3 and 120 hours, HR of group 4 was significantly higher than HR of the three other groups. However at 6, 24, and 72 hours when compared, HR of the four groups were not significantly different (p>0.05). Heart rates of the groups increased significantly (p<0.05) beyond their baseline values at 6, 24 and 72 hours post digital amputation. The pulse rate (PR) followed a similar trend as the heart rate. Significantly higher PR was recorded in group 4 compared to the other groups at 3 and 120 hours. The respiratory rate (RR) of the groups decreased significantly (p<0.05) below their baseline values in the intraoperative period and at 1 hour post-surgery (PS). The RR of the groups then increased significantly (p<0.05) at 24 and 72 hours PS. At 3 hours, group 4 also had a significantly higher RR (p<0.05) when compared with the RR of groups 1, 2 and 3. There was no significant difference in the peripheral capillary oxygen saturation (SPO2) between the different groups.

**Rectal temperature of the different groups**

There was no significant difference (p>0.05) between rectal temperature of the different groups. The rectal temperature (RT) of the different groups did not differ significantly (p>0.05) from their baseline value except RT of group 1 which significantly increased (p<0.05) at 6 and 24 hours as shown in Table 2.

**Serum biochemical parameters of the different groups**

As shown in Table 3 there was no significant difference (p>0.05) in the total protein, aspartate aminotransferase, urea, creatinine and bilirubin values of the animals in the different groups during the period of observation. The AST of group 2 was significantly lower (p<0.05) at 72 hours compared to its baseline reading while that of group 3 was lower than its baseline AST at 120 hours. The AST of group 4 was significantly lower (p<0.05) at 72 and 120 hours compared to its baseline values. Significantly lower (p<0.05) ALT levels was noted in all the groups at 72 and 120 hours (except group 1 at 120 hours). Group 3 and 4 had a significantly lower (p<0.05) urea level at 120 hours when compared to their baseline values. The serum creatinine and bilirubin levels of group 3 were significantly higher (p<0.05) at 24 hours when compared to the baseline values.

**Mean subjective pain scores of the different groups**

The pain scores of group 1 and 2 animals varied significantly (p< 0.05) from pain scores of group 3 and 4 at 1, 3, 6 and 24 hours post digital amputation. Group 1 also had a significantly higher pain score (p< 0.05) at 48 hours as shown in Table 4.

**DISCUSSION**

The main target of this work was to use a combination of drugs to achieve multimodal analgesia in dogs undergoing digital amputation. Xylazine an alpha-2 receptor agonist acts on both the peripheral and central nervous systems to produce sedation, analgesia and muscle relaxation (Ali and Al-Qarawi, 2002). This has encouraged its use in stress alleviation (Sanhouri et al., 1992). The decrease in the heart and pulse rate in the different groups intra-operatively and at 1 hour suggests an increase in vagal tone coupled with a decrease in sympathetic activity. This phenomenon and bradycardia can be caused by xylazine (Hayashi and Maze, 1993). Previously, reported effects of xylazine on the cardiovascular system include decreased sympatho-adrenal stimulation, decreased catecholamine release and reduced cardiac rhythmicity (Ali and Al-Qarawi, 2002). These observations were used to explain findings of earlier studies on the effect of α2- agonists on cardiovascular function. Literature search also showed that opioids cause cardiovascular depression by inducing a negative chronotropy and decreasing overall cardiac output (Stanley et al., 1980). Krakowski and Orebaugh (2015) had also reported that pentazocine caused a transient decrease in blood pressure along with reduced cardiac output which manifested clinically as a decrease in heart and pulse rate. Thus, decrease in heart rate and pulse rate of the different groups in this study may be attributed to the cardio-depressant effect of xylazine, tramadol and pentazocine.

The depression in respiratory rate observed in all the groups during the intraoperative period, might be attributed partly to the direct depression of the respiratory centres in the brain by some of the drugs used in the multimodal therapy. Pentobarbitone sodium like other barbiturate anaesthetic is a known respiratory depressant (Dai et al., 1983; Jun et al., 2012). Also, xylazine use in different animal species have been reported to result in respiratory depression (Singh et al., 2013). Opioid administration also causes respiratory depression and apnoea through a reduction of the sensitivity of the respiratory centre to carbon dioxide (Kurum et al., 2013). Pandey and Sharma (1986) had earlier observed respiratory depression in dogs injected with pentazocine. However, on the contrary, Torad and Hassan (2018), reported that pentazocine and tramadol given at the therapeutic doses unlike other opioid agents, did not cause severe respiratory depression. Similar to Torad and Hassan (2018), Natalini et al. (2007), also reported the lack of a clinically significant respiratory depression in the use of tramadol in human test subjects. The slight decrease in SpO2 in animals of all the groups may be attributed to vasoconstriction caused by xylazine as reported by Kuusela et al. (2000) and Leppanen et al. (2006) or have been brought about by the respiratory depression which was induced by the drugs (Maney, 2013). Despite the decrease in the peripheral capillary oxygen saturation (SpO2) levels of the various groups, SPO2 levels of the dogs did not vary significantly when compared with their baseline values. This suggests that the low dose of the drugs used induced anaesthesia with no associated apnea, an adverse effect often seen in α2 adrenoceptor agonist-opioid combinations (De Carvalho et al., 2016). The maintenance of peripheral capillary oxygen saturation (SpO2) near baseline at the intra-operative and immediate post-operative periods as recorded in the experimental dogs suggests that tissue perfusion was adequate in the subjects despite the respiratory depression caused by the drug combinations used.

Xylazine and pentobarbitone treatment has been shown to cause significant decrease in the rectal temperature of sedated transported goats (Biobaku, 2016) and in rats (Daemen et al., 1986). Xylazine mediated hypothermia was attributed to CNS depression in combination with a reduction in muscular activity and basal metabolic rate in the animals (Singh et al., 2009). It may also be due to the activation of alpha-2 receptor by xylazine, which mediate hypothermia (Lemke, 2004). Pentobarbitone sodium on the other hand is known to depress the autonomic nervous reflex system involved in blood pressure regulation and it may cause hypothermia. The resultant hypothermia might in turn decrease processes (metabolism, active transport) of drug distribution and drug elimination (Daemen et al., 1986). These findings are contrary to the findings of this work in which no significant temperature changes were noted. However, the observation made in this work was similar to that of Fayed et al. (2003), who reported a non-significant change in the temperature of stressed and unstressed cattle. Pentazocine being more closely associated to Mepridine has been shown to be resistive to some adverse changes which can bring about a decrease in RT (Ram et al., 2016).

In the post-operative period, significant increase in the heart rate occurred in all the groups at about 3 hours post digital amputation. This increase may be due to cardiovascular response to pain which lead to an increase in the activity of the autonomic nervous system or by compensatory sympatho-adrenal activation with catecholaminee release into the circulation following pain (Iwanaga, and Tsukamoto, 1997; Middleton, 2003; Astrid et al., 2005). This cardiovascular response might have occurred because at this time (3 h post-surgery), the plasma levels of the analgesics used might have dropped below the analgesic threshold thus allowing the onset of pain. This may also explain the increase in the pulse rate of the different experimental groups. Contrary to the results of the subjective pain scores obtained, group 4 which received CRI pentazocine showed a marked increase in the cardiopulmonary parameters from 3 hours up to 72 hours. According to Fukumitsu et al. (1987), pentazocine has a dose dependent action on the adrenal medulla which leads to catecholamine efflux. This catecholamine efflux might in turn cause an increase in the arterial blood pressure and other cardiopulmonary parameters of dogs anaesthetized with pentazocine (Takki et al., 1973). Pentazocine had also been reported to cause a dose and patient dependent increase in both heart rate and systolic blood pressure to an unpredictable and variable degree (Kucukhuseyin, 2003). The above findings from previous studies may explain the observed increase in HR of dogs which were given CRI pentazocine.

The serum biochemical parameters assayed served as a means of determining the effect of the drugs and there metabolites on the internal organs. Serum biochemical assays conducted for hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total protein [TP] and bilirubin) and renal function (urea and creatinine), showed that AST concentration increased in dogs in all groups by 24 h post-surgery. Serum AST level have been reported to be affected by hypoxia, anaesthesia induced stress and surgery (Davies, 1991) as well as cardiac, skeletal and hepatic cell damage (Harper, 1971). Tramadol is cleared by hepatic (cytochrome P450) and renal metabolism (Sandhu, 2010) while Pentazocine and xylazine are mainly metabolized in the liver. Hence the transient increase in AST level at 24 hours might be in response to hepatic metabolism of these drugs. AST serum levels in dogs however returned back to the normal physiological level indicating no long term undesirable effect on the liver. Igbokwe et al. (2012), had stated that pentazocine does not show hepatotoxic effects, thus supporting the findings of this study. Furthermore, bilirubin is the final by-product of haemoglobin degradation and serves as a diagnostic marker for liver or blood disorders (Fervery, 2008). The production of uncongugated bilirubin may be enhanced due massive haemoglobin breakdown as seen during haemolysis. In this clinical scenario, bilirubin production may be in excess of the livers ability to conjugate and excrete the pigment. Also, damage to the liver cells causes impairment of bilirubin excretion resulting in accumulation of bilirubin in the blood and extracellular fluid (Singh et al., 2013). Previuosly, diclofenac administration lead to elevation of conjugated bilirubin (Danan and Benichou, 1993; Benichou et al., 1993) and significant decrease in red blood cell count, haemoglobin and packed cell volume of goats (Abd Elazem and Abo-Kora, 2015). Inferring from these earlier findings, it can be suggested that elevated bilirubin levels recorded in all dogs in this study may indicate reduced liver function in dogs or may have been induced by diclofenac.

The outcome of this study showed that serum concentrations of creatinine increased in the immediate period post drug administration. The increase in creatinine level as recorded in this study may be partly attributed to the inhibitory effect of the anaesthetic drug-pentobarbitone on the renal blood flow, leading to increased serum accumulation of creatinine which is a by-product of muscle damage and amino acid degradation (Singh et al, 2013). In addition, pentazocine use has also been associated with elevated creatinine levels (Igbokwe et al., 2012) while on the contrary, the report of McMillan et al. (2008) showed that dogs injected intravenously with tramadol at doses of 1, 2, and 4 mg/kg demonstrated insignificant changes in this parameters. Hence, transient changes in serum creatinine level in the dogs may be due to the effect of pentazocine and pentobarbitone used in multimodal drug regimen. .

The result of the subjective pain score showed that group 3 and 4 had a significantly lower value than group 1 and 2. This may be as a result of the xylazine-opioid synergism reported by Taqa (2012). The efficacy of pentazocine as an analgesic has been reported by several studies (Neeraj et al., 2016; Yadav and Gupta, 2016). In addition, a study conducted by Udegbunam et al. (2014), demonstrated the efficacy of tramadol as a potent analgesic for post-operative pain. Despite an earlier report that tramadol produced better labour pain relief than pentazocine in human paturients (Nagaria and Acharya, 2006), this study showed that analgesia was better in pentazocine treated dogs when compared to the tramadol group. This may be suggestive of a greater potentiation of the analgesic properties of pentazocine by xylazine when compared to that with tramadol at the doses used for this study.

It can be concluded from this study that pentazocine-xylazine CRI provided better analgesia when compared to xylazine CRI and tramadol-xylazine CRI. Based on this, the use of xylazine and pentazocine can be recommended in multimodal analgesic protocols in orthopaedic surgery cases. The observed elevation in serum bilirubin and creatinine levels suggests that serum concentration of these analytes may be raised following the use of the drug combinations tested. However further work may be conducted using different doses of the drugs in order to establish the safety margin of the combination.

**Conflict of Interest**

The authors declare that they have no competing interests.

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**Table 1:** Mean ± SE value of heart rate (bpm), pulse rate (bpm), respiratory rate (cpm) and peripheral capillary oxygen saturation (%) at different time intervals of observation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Groups** | **1** | | **2** | **3** | **4** |
| **HEART** | **Baseline** | 82.67±3.53a | | 80.00±20.53a | 90.00±2.00a | 112.00±20.00a |
| **RATE** | **IntraOp** | 54.00±7.57a | | 54.67±6.67a | 60.00±20.00a | 67.00±1.00a |
| **(bpm)** | **1hour** | 78.67±20.70a | | 64.00±9.24a | 48.00±4.00 a | 78.00±2.00a |
|  | **3hours** | 102.67±7.06ab | | 112.67±10.35ab | 86.00±14.00a | 140.00±20.00b |
|  | **6 hours** | 114.67±13.53a\* | | 125.33±18.81a\* | 110.00±18.00a\* | 170.00±30.00a\* |
|  | **24 hours** | 112.00±16.17a\* | | 133.33±22.19a\* | 118.00±26.00a\* | 175.00±5.00a\* |
|  | **72 hours** | 124.00±6.11a\* | | 125.33±23.13a\* | 116.00±20.00a\* | 152.00±24.00a\* |
|  | **120 hours** | 89.33±7.42a | | 104.00±20.00a | 112.00±8.00ab | 158.00±6.00b |
| **PULSE** | **Baseline** | 74.67±7.06a | | 75.67±7.92a | 73.50±2.00a | 115.00±27.00a |
| **RATE** | **IntraOp** | 45.17±8.90a | | 49.17±9.73a | 54.00±21.00a | 50.75±9.75a |
| **(bpm)** | **1 hour** | 64.67±5.36a | | 50.53±8.12a | 40.05±3.95a | 56.75±9.75a |
|  | **3 hours** | 92.00±13.14a\* | | 92.83±10.31a\* | 66.00±2.00a | 136.75±5.25b\* |
|  | **6 hours** | 104.37±14.66a\* | | 106.83±16.79a\* | 105.75±17.75a\* | 132.50±10.00a\* |
|  | **24 hours** | 103.00±21.22a\* | | 125.67±24.11a\* | 100.50±37.00a\* | 170.50±2.50a\* |
|  | **72 hours** | 102.00±18.18a\* | | 118.00±23.18a\* | 110.00±18.00a\* | 144.00±24.00a\* |
|  | **120 hours** | 68.33±7.19a | | 93.20±14.68a | 85.25±11.75a | 147.50±1.00b |
| **RESP.** | **Baseline** | 32.00±4.00a | | 40.00±12.22a | 28.00±0.00a | 38.00±2.00a |
| **RATE** | **IntraOp** | 20.00±4.00a\* | | 14.67±1.33a\* | 14.00±2.00a\* | 18.00±2.00a\* |
| **(cpm)** | **1 hour** | 20.67±2.91a\* | | 16.00±2.31a\* | 14.00±2.00a\* | 16.50±7.50a\* |
|  | **3 hours** | 24.00±4.00ab\* | | 24.00±2.31ab\* | 18.00±2.00a\* | 30.00±2.00b\* |
|  | **6 hours** | 29.33±3.53a | | 29.33±2.67a | 34.00±2.00a | 50.00±18.00a |
|  | **24 hours** | 38.00±3.46a\* | | 45.33±7.42a\* | 54.00±6.00ab\* | 74.00±14.00b\* |
|  | **72 hours** | 36.00±2.31a\* | | 45.33±7.42a\* | 44.00±12.00a\* | 58.00±6.00a\* |
|  | **120 hours** | 32.00±2.31a | | 26.67±3.53a | 32.00±4.00a | 36.00±0.00a |
| **SPO2** | **Baseline** | | 94.00±1.73a | 96.67±0.88a | 95.00±3.00a | 97.00±2.00a |
| **(%)** | **IntraOp** | | 93.67±1.86a | 93.33±2.67a | 93.50±2.50a | 96.00±2.00a |
|  | **1 hour** | | 93.67±1.45a | 92.67±5.33a | 94.50±1.50a | 95.00±3.00a |
|  | **3 hours** | | 94.67±1.76a | 92.67±2.85a | 83.50±11.50a | 95.50±1.50a |
|  | **6 hours** | | 96.33±0.88a | 92.33±2.60a | 94.50±1.50a | 96.00±1.00a |
|  | **24 hours** | | 96.00±1.73a | 90.00±5.69a | 90.50±2.50a | 94.50±1.50a |
|  | **72 hours** | | 94.67±1.67a | 91.67±3.28a | 88.00±5.00a | 95.00±1.00a |
|  | **120 hours** | | 89.00±4.36a | 89.00±4.51a | 85.50±4.50a | 94.00±4.00a |

Different superscriptsa,b in rows indicate a significant difference at p<0.05.

Superscripts \* in columns indicate a significant difference from baseline reading of the group at p<0.05

**Table 2:** Mean ± SE value of temperature (ºC) at different time intervals of observation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Groups** | **1** | **2** | **3** | **4** |
| **TEMP.** | **Baseline** | 36.97±0.43a | 37.90±0.60a | 37.70±0.10a | 37.80±0.80a |
| **(ºC)** | **IntraOp** | 38.03±0.09a | 38.30±0.23a | 38.45±0.65a | 37.80±0.00a |
|  | **1 hour** | 37.40±0.21a | 37.73±0.64a | 38.25±0.55a | 38.30±0.20a |
|  | **3 hours** | 38.10±0.12a | 38.83±0.12a | 37.70±1.20a | 37.60±0.60a |
|  | **6 hours** | 38.63±0.52a\* | 38.83±0.41a | 38.85±0.05a | 38.25±0.35a |
|  | **24 hours** | 38.33±0.13a\* | 39.03±0.53a | 38.95±0.05a | 38.10±0.30a |
|  | **72 hours** | 37.57±0.54a | 38.03±0.91a | 38.85±0.15a | 37.55±0.25a |
|  | **120 hours** | 38.03±0.46a | 37.80±0.35a | 37.35±0.05a | 37.05±0.35a |

Different superscriptsa,b in rows indicate a significant difference at p<0.05.

Superscripts \* in columns indicate a significant difference from baseline reading of the group at p<0.05

**Table 4:** Mean ± SE value of serum biochemical parameters at different time intervals of observation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Groups** | **1** | **2** | **3** | **4** |
| **TP** | **Baseline** | 5.73±0.50a | 8.28±1.60a | 5.94±0.04a | 8.23±0.17a |
| **g/dl** | **24 hours** | 6.31±0.38a | 7.10±0.69 a | 7.33±0.27 a | 8.25±0.61 a |
|  | **72 hours** | 4.93±0.52 a | 5.60±0.13 a | 6.62±1.35 a | 6.96±0.61 a |
|  | **120 hours** | 6.27±0.69 a | 6.31±1.47 a | 5.98±0.17 a | 6.27±0.25 a |
| **ALT** | **Baseline** | 75.36±10.27 a | 68.54±9.62 a | 57.02±16.90 a | 64.63±4.79 a |
| **µ/l** | **24 hours** | 53.95±10.70 a | 64.03±10.37 a | 57.77±20.47 a | 64.54±15.03 a |
|  | **72 hours** | 35.62±6.01 a\* | 28.04±6.09 a\* | 19.00±6.11 a\* | 20.97±5.07 a\* |
|  | **120 hours** | 44.91±0.10c | 31.53±2.90b\* | 11.11±5.92 a\* | 12.80±1.79 a\* |
| **AST** | **Baseline** | 76.04±3.69 a | 110.00±21.00 a | 62.79±12.24 a | 96.18±24.22 a |
| **µ/l** | **24 hours** | 99.83±12.52 a | 126.68±20.15 a | 80.00±5.35 a\* | 132.64±44.87 a |
|  | **72 hours** | 58.70±12.03 a | 47.32±6.34 a\* | 56.92±3.82 a | 50.80±5.87 a\* |
|  | **120 hours** | 72.98±19.91 a | 83.86±37.00 a | 36.53±1.28 a | 34.23±1.02 a\* |
| **UREA** | **Baseline** | 15.49±6.69 a | 26.50±10.47 a | 50.18±21.73 a | 31.45±3.36 a |
| **(mg/dl)** | **24 hours** | 30.39±4.88 a | 22.32±2.70 a | 28.45±9.19 a | 22.26±1.06 a |
|  | **72 hours** | 33.49±2.92 a | 28.45±2.01 a | 48.60±25.09 a | 21.64±4.86 a |
|  | **120 hours** | 23.47±11.79 a | 33.51±9.43 a | 18.82±0.98 a\* | 16.96±1.59 a\* |
| **CREA.** | **Baseline** | 0.63±0.61 a | 0.41±0.15 a | 0.72±0.00 a | 0.14±0.00 a |
| **(mg/dl)** | **24 hours** | 0.78±0.57 a | 1.53±1.46 a | 2.27±0.04 a\* | 0.45±0.05 a |
|  | **72 hours** | 1.21±0.53 a | 1.16±0.17 a | 0.65±0.11 a | 0.35±0.05 a |
|  | **120 hours** | 1.26±0.00 a | 0.70±0.30 a | 0.61±0.25 a | 0.60±0.42 a |
| **BIL.** | **Baseline** | 1.48±0.73 a | 0.11±0.04 a | 0.21±0.02 a | 0.35±0.21 a |
| **(mg/dl)** | **24 hours** | 1.83±1.03 a | 0.86±0.37 a | 3.90±0.00 a\* | 0.73±0.67 a |
|  | **72 hours** | 1.19±0.75 a | 1.97±0.88 a | 1.20±1.08 a | 0.88±0.35 a |
|  | **120 hours** | 2.27±1. 66 a | 2.04±0.66 a | 1.28±0.21 a | 1.11±0.12 a |

Different superscripts a,b,c in rows indicate a significant difference at p<0.05. . Superscripts \* in columns indicate a significant difference from baseline reading of the group at p<0.05

**Table 5:** Mean subjective pain score values at different time intervals of observation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Groups** | **1** | **2** | **3** | **4** |
| **PAIN** | **1 hour** | 7.00b | 7.00b | 4.00a | 2.50a |
| **SCORE** | **3 hours** | 6.67b | 6.67b | 3.50a | 4.00a |
|  | **6 hours** | 6.17b | 6.83b | 4.50a | 3.50a |
|  | **24 hours** | 8.33b | 6.00b | 3.00a | 3.00a |
|  | **48 hours** | 9.00b | 4.00a | 4.00a | 4.00a |
|  | **72 hours** | 5.50a | 5.50a | 5.50a | 5.50a |

Different superscripts a,b in rows indicate a significant difference at p<0.05