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MULTIMODAL APPROACH TO SURGICAL PAIN MANAGEMENT IN WEANER PIGS - A CLINICAL TRIAL.

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1. INTRODUCTION Pain is an unpleasant sensory and emotional feeling accompanying existing or impending tissue damage or referenced to such damage (IASP, 2014). It is caused by irritation of the receptors, called nociceptors. Nociceptors are free nerve endings that respond to painful stimuli. Stimulated by chemical, biological, electrical, mechanical, and thermal stimuli they transmit information to the brain. When stimuli are transmitted to the spinal cord, then to the central areas of the brain, pain perception occurs. When tissue damage occurs, chemical mediators such as histamine, bradykinin, substance P, acetylcholine, leukotrienes that modulate the transmission of pain are released into the extracellular tissue. Mediators can produce other reactions, such as vasoconstriction, vasodilatation, or altered capillary permeability at the site of injury (Porter, 2013). Opioid analgesics (morphine, fentanyl, alfentanil, sufentanil, meperidine, tramadol) play an important role in the acute treatment of moderate to severe pain in the early postoperative period. Routes of administration includes intravenous, intramuscular, subcutaneous, epidural, transmucosal, intrathecal, transdermal. Patient controlled analgesia optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamics variability in individual patients (Ronald et al., 2009). Non-opioid analgesics are increasingly being used before, during, and after surgery to facilitate the recovery process. The use of traditional non steroidal anti-inflammatory drugs – NSAIDs (aspirin, ibuprofen) (Ong et al., 2010), cyclooxygenase-2 (COX-2) inhibitors, acetaminophen (Chou et al., 2016), adjuvants such as alpha-2 adrenergic agonists (dexmedetomidine) (Blaudszun et al., 2012), gabapentin-type drugs (gabapentin, pregabalin) (Clarke et al., 2012), and glucocorticoid steroids (dexamethasone) (Salerno and Hermann, 2006) can provide beneficial effects when administered in appropriate doses as part of a multimodal analgesic regimen in the perioperative setting (Elvir Lazo & White, 2010). Multimodal analgesia refers to the practice of concurrent application of combination of analgesic agents and different techniques that act by different mechanism to target different points along the pain pathway resulting in additive or synergistic analgesia with lowered adverse effects of sole administration of individual analgesics (Leigh, 2008; Buvanendran & Kroin, 2009; Elvir Lazo & White, 2010). It was developed following advances in the knowledge of molecular mechanisms. Ideally, pain involves multiple mechanisms that require treatment using a balanced (or ‘multimodal’) analgesic technique (White & Kehlet, 2010). Principles of a multimodal strategy include control of postoperative pain to allow early mobilization, early enteral nutrition, education, and attenuation of the perioperative stress response. The approach involves administering a combination of opioid and non-opioid analgesics (and adjuvant agents) that act at different sites within the central and peripheral nervous systems to improve pain control, with fewer opioid-related side effects mainly drowsiness and sedation, constipation, nausea, vomiting, pruritis, ventilator depression (Elvir Lazo & White, 2010; Vadivelu et al., 2010). Millions of surgeries are performed on an annual basis, necessitating the frequent use of acute pain management. There are many types of surgery and, with few exceptions, presenting with different degree of pain. Newer drugs, techniques and protocols for pain management have been developed, and minimally invasive surgical techniques, such as endoscopic procedures, are used more frequently (Cornwell, 2013). Unrelieved pain has harmful effects to multiple body systems. Implementing multimodal pain management improves pain relief during hospitalized stay, improves patient satisfaction, and reduces the overall opioid consumption after orthopedic surgeries (Kang et al., 2013). This study thus aims to evaluate the effects of multimodal approach to pain response in weaned pigs presented for different soft tissue surgical conditions.

2. MATERIALS AND METHODS

Animals and Housing Two female and one male piglet aged, 4 months with an average weight of 18.0 ± 8.96kg were brought in from the College farm, College of Veterinary Medicine, Federal University of Agriculture, Abeokuta. They were provided with feed and water ad-libitum. They were fasted for food overnight before surgery but had water ad-libitum in each case. Induction, Maintenance and Monitoring of Anesthesia The animals were clinically examined (general condition, physiological parameters- heart rate, rectal temperature). Venous access was achieved through the auricular vein, with an infusion pump (Hawkmed™, Wellkang Ltd., China). Lactated ringer’s solution was instituted at 10mlkghr-1 to maintain homeostasis during anesthesia. Each weaned piglet received 0.05mgkg-1 1% atropine, and 0.01mgkg-1 dexmedetomidine (Orion Pharma Ltd, Dhaka, Bangladesh) as premedication at two minutes apart. Induction was achieved with 10mgkg-1 ketamine, intubation was carried out with size 7.5ID endotracheal tube (D Notec®, UK). Thereafter, 200µgkg-1 butorphanol (MSD Animal Health, UK) and 0.03mgkg-1 buprenorphine (Dechra Pharma, USA) were administered at fifteen minutes apart respectively for analgesia, all drugs were given intramuscularly. Anesthesia was maintained with continuous rate infusion of ketamine at 5mgkghr-1 using a syringe pump (Practivet®, Phoenix). Monitoring The blood glucose level and hematological assessment was done before and after surgical procedure; using blood glucose meter (On Call Plus, ACON Labs, USA) and the Mindray haemoanalyzer respectively. The physiological variables (heart rate, respiratory rate, pulse rate, peripheral capillary oxygen saturation and rectal temperature) were being monitored continuously on a 5-lead multiparameter patient monitor (General Meditech Inc., China) and records were taken before surgery and every fifteen minutes throughout the surgical period. The average time of surgery, some anesthetic indices and side effects (if any) were also noted. Surgical Preparations The surgical sites of the three weaned piglets were prepared aseptically with 0.05% Chlorhexidine solution. Following general anesthesia, the pigs was positioned in dorsal, left lateral and right lateral recumbency and draped for ovariohysterectomy, enterectomy and radical left nephrectomy, respectively. Ovariohysterectomy (OVH) Technique Ventral mid-line incision of about 10cm was made from just caudal to the umbilicus toward the pelvic brim. The subcutaneous fat was dissected bluntly with a blunt scissors to expose the linea-alba. A horn of the uterus was located with a finger within the abdominal cavity. The uterine horn was traced to the ovary. The ovarian pedicle was ligated with chromic catgut absorbable suture size 0. The uterus was then followed to the contralateral ovary which was also ligated and transected. The body of the uterus was then ligated with trans fixation and circumferential sutures caudal to the cervix. The uterus and ovaries were then removed, and all ligatures were examined closely for any hemorrhage. The incision was then closed in three layers. The linea-alba was closed with double rows of simple continuous suture pattern using size 1 catgut. The subcutaneous tissue was closed with subcuticular pattern using size 1 chromic catgut, while the skin was closed with horizontal mattress suture pattern with size 1 nylon monofilament. Routine incision observation and surgical care were practiced. The surgical procedure lasted for one hour forty-five minutes. The piglet was confined for a few days to limit activities that might stress the abdominal incision and recovered without any complication. Enterectomy; end-to-end anastomosis Technique A modified grid incision of about 10cm was made vertically on the right flank. The desired gut region was brought sufficiently extra-abdominally to allow resection and to prevent peritoneal contamination from intestinal contents. After the extent of resection was determined, the vessels of the adjacent mesentery were ligated; the mesentery to be removed was wedge-formed. The blood supply of the proposed sites of resection was not compromised. The proposed jejunum was isolated by carefully placing two pairs of intestinal clamps over adjacent bowel. The mesentery was transected distal to the ligatures, and the demarcated loop was resected between the two clamps, both proximally and distally. The cut ends were flushed with physiologic saline and apposed, with the lumina held toward the surgeon using an ‘end-to-end’ anastomosis technique. Chromic catgut absorbable suture material size 0 was used for the two suture lines. After removal of the clamps the intestine was flushed again, and the anastomosis was checked for patency and leakage. The defect in the mesentery was closed with interrupted sutures. The intestine was returned into the abdomen and 5 mL of Penicillin streptomycin (PenStrep®, Kepro, Holland) was infilterated and the laparotomy wound was closed routinely in four layers. Peritoneum, transversalis fascia and transversus muscle were sutured together in a simple continuous pattern using size 1 catgut. The internal oblique muscle was sutured with three simple interrupted sutures. The external oblique muscle was also closed with four simple interrupted sutures using size 1 catgut. The skin was closed with horizontal mattress suture pattern with size 1 nylon monofilament. Routine incision observation and care were practiced. Enterectomy; end-to-end anastomosis lasted for one hour fifty-five minutes. Dietary measures were routinely taken. Radical Left Nephrectomy (RLN) Technique An extra-peritoneal flank approach was used. A 10cm incision in a line 1cm lower to the most ventral rib was made. The four muscle layers were divided by sharp dissection in the direction of the incision until the peritoneum was reached. A self –retaining retractor was used to keep the wound edges separated. The peritoneum was elevated off the posterior abdominal wall by blunt dissection. The ureter was identified and followed all the way to the level of the renal hilum. All the attachments medial to the ureter were isolated and alienated. The lateral and posterior renal attachments were released, allowing the kidney to rotate medially. The kidney was rolled anteromedially to allow dissection of the renal hilum. Thereafter, the remaining attachments to the kidney were located superiorly; likewise, the superior, medial, and posterior attachments of the adrenal were also released to remove the adrenal gland. The ureter and all remaining attachments were separated, and the specimen was removed. The muscles were closed in layers with a continuous size 0 absorbable suture and the skin with a horizontal mattress 1 non-absorbable suture. All sutured pedicles were checked for adequate hemostasis before closure. The procedure lasted for two hours. There were no complications in the immediate post-operative period. Postoperative Care Meloxicam was administered intramuscularly at 0.4mgkg-1 immediately post surgery. Atipamezole (Dechra, The Netherlands) at 0.01mgkg-1 was administered intramuscularly as reversal for dexmedetomidine at the end of the surgery in all cases. Pain medications and systemic antibiotics were also administered as needed. The weaner pigs were each returned to the holding pen post full recovery from anesthesia. The animal was re-established on feed within 72 hours postoperatively. Removal of stitches was done fourteen days post-surgical procedure in all patients. Calculations of anesthetic indices Quality of induction: This was defined as the time interval (in minutes) between premedication and successful insertion of endotracheal tube. Duration of Anesthesia: This was defined as the time interval (in minutes) between loss of swallowing reflex and return of same. Quality of Analgesia:This was defined as poor, fair, good, very good and excellent based on significant differences in physiological parameters measured Recovery time: This was defined as the time interval (in minutes) between injection of atipamezole and standing positions. Statistical analysis Results were expressed as mean ± SD. The blood glucose level and hematological parameters were analyzed using student’s T test for paired data and subjected to post hoc test using Mann Whitney’s test. The cardiopulmonary parameters were analysed using Least Significant Difference (LSD). P value ≤ 0.05 was considered significant in all cases.

3. RESULTS

Physiological Changes No significant differences were observed in the heart rate (HR), pulse rate (PR), peripheral capillary oxygen (SpO2) and rectal temperature (RT) but with a significant difference in respiratory rate (RT) (Table 2). The reduction observed in the blood glucose level was not statistically significant, p=0.7 (Table 3) Hemodynamic changes Hematological findings in Pig 1 showed moderate anemia, microcytic but hyperchromic due to excessive hemolysis post anesthesia and moderate leukopaenia (Table 5). In pig 2, there was mild anemia, but also normocytic hyperchromic due to excessive hemolysis with marked leukopaenia post anesthesia(Table 6). And Pig 3 showed mild thrombocytopenia and moderate increase in erythropoiesis post anesthesia (Table 7).

4. DISCUSSION

Pain management is an important welfare issue for veterinarians, investigators, and pet owners alike (Turner et al., 2006). A multimodal approach to pain management is most effective especially when the individual analgesic agents act through different analgesic mechanisms and act synergistically (Gregg et al., 2013). Multimodal analgesia using adjuvant analgesics such as antidepressants antiepileptic drugs, NMDA antagonist (ketamine) or transdermal lidocaine may also be effective alternative for the treatment of refractory chronic pain unresponsive to the administration of a single agent (Knotkova and Pappagallo, 2007). It has been reported that by activating multiple pain inhibitors pathways (transduction, transmission, modulation of spinal pathways and perception), combination analgesics can provide more effective pain relief for broader spectrum of pain and may also reduce the adverse drug reaction (Gregg et al., 2013). The use of atropine sulphate (an anticholinergic drug) was to reduce hypersalivation and bradycardia induced by ketamine, in agreement with Wellington et al., 2013. Moreover, atropine produces sedation by crossing the blood-brain-barrier (Lu et al., 2014). Ketamine is an N-methyl-D-aspartate antagonist is acting to potentiate the analgesic effect of the opioids and α2 agonist. NSAIDs (meloxicam) are one of the classes of drugs used to prevent and treat postoperative pain in animals. The choice of the dose of meloxicam used (0.4mgkg-1 ) is in agreement with the work of Schmidt and Banting (2000), they demonstrated the efficacy and safety of a single treatment of 0.4mgkg-1 meloxicam and confirmed it as the recommended dose for the treatment of a variety of conditions associated with inflammation and infections in pigs. Behavioral indicators as well as physiological measures are useful biomarkers of pain (Ison et al., 2016). In this study, both behavioral and physiological measurements were used to assess pain. The analgesia was judged to be very good based the uneventful recovery of the patient from anesthesia. This agrees with the expected painful behavioral patterns which include posture, gait, tremors, spasm (quick, involuntary muscle contractions), stiffness (lying with extended, tensed legs), prostration (sit or stand motionless, head down) and restlessness by observations of the pigs before, during, and after surgical procedures as described by Karriker et al., 2013; Mohling et al., 2014; Wilson et al., 2014; Ison et al., 2016. Also lying behavior is an important thermoregulatory mechanism in pigs. When the temperature lowers, they adapt their behavior by huddling and lying down (Dekker, 2015). And the relatively stable physiological parameters measured in this study which agrees with the report of Hansson et al., 2011. They reported that increase in heart and respiratory rates and a decrease in skin temperature are part of the responses of the sympathetic adrenomedullary (SA) system and the autonomic nervous system (ANS), involved in mobilizing the body for “fight-or-flight,” constricting blood vessels, dilating blood vessels for muscles in painful conditions. Pulmonary depression was observed in this clinical trial, this may be because of the opioids used in the clinical trial. The anemia recorded in the present study might have resulted from hemorrhage arising from the surgical procedure although higher doses or prolong use of NSAIDs causes serious erosive gastritis and gastric hemorrhage due to decrease in the amount of prostaglandin PGE2 and PGI2 (Venkat et al., 1998) and inhibition of platelets aggregation (Raffa, 2001). The leukopenia recorded in the present study have been reported by various workers (Galley et al., 2000; Kona-Boun et al., 2005; Schneemilch et al., 2005; Homburger and Meier, 2006; Knotkova and Pappagallo, 2007). Opioid receptors are found on cells of the immune system and opioid effects on immune function vary from stimulation to inhibition (Page et al., 2001; Stefano et al., 2005). While thrombocytopenia observed in the present study may also be attributed to the inhibition of platelets production by NSAIDs (Venkat et al., 1998; Raffa, 2001)

5. CONCLUSION

The NMDA antagonist, opioids and α2 agonist are suitable for treatment of both acute and chronic pain of a mild to moderate degree. The anti-inflammatory and synergistic actions of NSAID with opioids was favorable during the postoperative pain management. In the present study, the use of combination of different analgesics in clinical cases showed a favorable outcome with most physical parameters within normal range. However, care must be taken in terms of dosage and duration of treatment since large dosage and prolonged usage can lead to adverse hematological changes.