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Stem Cell Research 2018-Effect of Stress Induced by Anesthesia and Surgery on Peripheral Blood Mobilization of Stem Cells in Horses- Jishnu Rao Gutti- Madras Veterinary College

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Introduction

Stem cell mobilization is a process by which the HSCs, Endothelial Progenitor Cells (EPCs) and MSCs from the bone marrow are mobilized to the periphery and available for further therapeutic procedures. The functions and regulation of HSCs within the niche is based on a highly complex process involving not only intrinsic cues within the HSC themselves but signaling from the surrounding microenvironment in which they reside. Disruption of one or more of these niche interactions can result in the release of HSCs from the niche and their trafficking from the bone marrow to the peripheral circulation, a process termed peripheral blood stem cell mobilization. Mobilization can be achieved through administration of chemotherapy hematopoietic growth factors, chemokines, and small-molecule chemokine receptor inhibitors or antibodies against HSC niche interactions. Anesthesia and surgery increase endogenous catecholamine as a response to the activity of sympathetic nervous system due to nocifensive response to surgery and a wider stress response to anesthetic-induced stress and hypoxia. Stress-induced signals activate neutrophils and osteoclasts which in turn cause shedding and release of membrane-bound Stem Cell Factor (SCF), the proliferation of HSC and play a major role in stem cell mobilization. The host immune system response to inflammation increases the release of leukocytes that include HSC from the bone marrow . MSCs and HSCs are used for stem cell therapy/ regenerative therapy in equines for the management of tendon injury, osteoarthritis, wound healing and other degenerative disorders. No studies were available on the extent of mobilization of HSCs and MSCs following anesthesia in horses to predict the volume of peripheral blood to be collected for the collection of a required number of stem cells by ficoll gradient density method or apheresis for therapy. The study included evaluation of the plasma cortisol level, stress leukogram and mobilization of peripheral blood HSCs/progenitor cells as a response to stress during total intravenous anesthesia using the midazolamketamine mixture in butorphanol-dexmedetomidine-acepromazine pre-medicated horses and compare with ketamine in butorphanolxylazine pre-medicated horses for surgery.

Methods

The clinical study was conducted on horses of either sex referred for elective surgical procedures warranting general anesthesia as approved by the Dean of Clinics and The Dean, Faculty of Veterinary Sciences, Tamil Nadu Veterinary and Animal Sciences University, India. On admission, the horses were subjected to pre-operative check-up that included physiological observations, complete hematology, and serum biochemical analysis. The American Society of Anesthesiologists (ASA) classification [7] was followed to categorize the health status of the horses. The 12 horses selected on basis of ASA 1 status were randomly allotted to group I and group II each consisting of 6 horses. The feed was withheld for 12 hours but not water prior to anesthesia. All the trials were conducted in the forenoon to avoid diurnal variations. All the horses in group I and II were pre-medicated with butorphanol (0.01 mg/kg BW) intravenously. After 20 minutes, group I horses were administered with dexmedetomidine (5.00 µg/kg BW) intravenously followed by acepromazine (0.03 mg/kg BW) intravenously 15 minutes later. Group II horses were administered with xylazine (1.10 mg/kg BW) intravenously 20 minutes after the administration of butorphanol. At peak sedation, the horses were induced with a mixture of ketamine hydrochloride and midazolam, administered intravenously at the dose rate of 2.00 and 0.05 mg/kg body weight respectively in group I horses and ketamine alone at a dose rate of 2.20 mg/kg in group II horses. Further maintenance was carried out with the same combinations in the respective groups of horses. Plasma cortisol level was assessed pre-operatively, intraoperatively, post-operatively and after 24 hours of surgery, 2nd, 4th

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and 6th postoperative days. The plasma cortisol estimation was analyzed based on direct immune enzymatic method and values were estimated in ng/dl. Stress leukogram was assessed pre-operatively, intraoperatively, post-operatively and after 24 hours of surgery, 2nd, 4th and 6th postoperative days. The mean total leukocyte count (thousand/mm3) and differential count (%) were estimated by auto-hemolyser.

Results and Discussion

Plasma cortisol level was assessed pre-operatively, intra-operatively, post-operatively and after 12 hours of surgery and the statistical analysis revealed no significant difference between both the groups of horses (Table 1) but uniformly, highly significant increase could be observed following sedation and declined to normal on 6th postoperative day. The stress response to surgery and anesthesia was characterized by increased secretion of the pituitary hormones and the activation of the sympathetic nervous system. The changes in the pituitary hormones secretion had a secondary effect on hormone secreted from target organs-released corticotropin from the pituitary stimulated cortisol secretion from adrenal cortex [19]. The present study showed a significant increase in the plasma cortisol value during the post-operative period in horses that were pre-medicated with xylazine-butorphanol, induced and maintained with ketamine alone when compared with horses that were pre-medicated with dexmedetomidine-acepromazine-butorphanol, induced and maintained with ketamine-midazolam which concurred with the findings of Prunier, et al. [20], Carroll, et al. [21], Prunier, et al. [22] and Moya, et al. [23] who opined that it was due to the activation of the hypothalamic-pituitary-adrenal axis and also due to xylazine and ketamine anesthesia which was attributed to decreased breakdown of plasma cortisol caused by reduction in hepatic blood flow during surgery and therefore elevated the plasma half-life of cortisol [11,24- 28]. The gradual decrease in plasma cortisol level in the post-operative period and return near to base value after a week could be attributed the use of analgesics. The findings of the current study concurred with Davis, et al. [3], Nogueira, et al. [26], Roth, et al. [29], Robertson, et al. [30] and Montane, et al.

Conclusion:

The present study revealed that the magnitude of stress response was higher in terms of stress leukogram and plasma cortisol level in horses undergone induction and maintenance with ketamine alone when compared with ketamine and midazolam and uniformly the stress parameters elevated following sedation. The percentage of cells expressing CD34 marker increased only on the 6th postoperative day in both the regimens and cells expressing CD105 did not show any variation revealing mobilization of HSCs occurred only during reparative and healing process; rather than as a response to stress. All the animals were subjected to anesthesia and surgery, hence could not be definitely be concluded that whether the mobility of HSCs was associated with post-anesthetic stress or post-surgical stress and it would be more appropriate to conclude that the mobilization of HSCs could be due to the reparative process towards the tissue insult caused by surgery.

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