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Hormonal response and reproductive performance of crossbred rabbit does (*Oryctolagus cuniculus*) fed dietary niacin supplementation under heat stress conditions

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***Targeted Audience:** Feed producers and rabbit farmers*

Abstract

Effect of dietary niacin supplementation was investigated on hormonal response of crossbred rabbit does (Oryctolagus cuniculus) in a 6-week feeding trial. A total of 30 matured rabbit does of 18 to 20 weeks old with average weight of 2.75 kg were used. Niacin was included in the diets of the rabbits at levels of 0 (control), 50, 100, 150 and 200 mg/kg feed. The rabbits were randomly allotted to the diets (n=6 rabbits/treatments) and housed individually. Data generated were subjected to analysis of variance while the significant differences in means were separated using pairwise-difference. Results showed that rabbit does fed dietary niacin at 100, 150 and 200 mg niacin/kg diet had significantly (P<0.05) higher oestradiol (26.02, 26.25, 26.40 vs. 24.84 pg/ml) and progesterone (8.18, 8.76, 8.90 vs. 7.63 ng/ml) concentrations as well as litter size at birth (7.50, 8.50, 7.90 vs. 6.20) and at weaning (6.80, 7.45, 7.10 vs. 5.00) than their counterparts fed the control diet. There was significant interaction between niacin levels and breeding periods on oestradiol and progesterone concentrations of the does. The results of this study suggest that feed grade niacin supplementation at 100, 150 and 200 mg niacin/kg diet could potentially improve hormonal profile which led to improved litter size at birth and at weaning of the rabbit does.

Key words: Niacin, rabbits, hormone, litter performance

Description of problem

Rabbits are challenged by different stressors from their immediate environment resulting in the development of varying degrees of responses (1). Oxidative stress causes damage to biological molecules (2), depletes antioxidant scavenger system in the blood and kidney (3), disturbs normal cell functions and initiates chain reactions that can compromise cell integrity (4). It is involved in mammary gland inflammations (5), kidney dysfunction and its impairment (6), atherosclerosis (7) and causes intestinal permeability dysfunctional process (8). It also causes impaired reproductive performance of farm animals (9). It causes defective embryonic development (10) and embryonic damage (11). It causes female infertility (12) and inhibits progesterone synthesis in breeder cows (13). Niacin-mediated reduction in ROS was associated with significant inhibition of NADPH oxidase, a key enzyme involved in ROS production. Ganji *et al*. (14) suggested that niacin, through inhibiting NADPH oxidase may decrease ROS generation in hepatocytes. Niacin induces cutaneous vasodilation/flushing, a vasodilatory response induced by relaxing the blood vessels which results in increased blood flow under heat stress (15) conditions. Niacin has been indicated to play a dual role in regulating the increased synthesis of heat shock proteins (HSPs) that are crucial in ameliorating heat stress (16).

Anti-oxidative mechanisms in animals are activated to cope with steroidogenesis-dependent oxy-radical formation in the corpus luteum (17). They regulate major changes during the oestrous cycle (18), involve in the preservation and capacitation of sperm cells (19) and maintain corpus luteum function of placental luteotrophins (20). They also play a key physiological role in the successful fertilization and implantation *in vivo* and reduce retained foetal membranes (21). They improve the quality and meiotic oocyte maturation rate in rabbits (22). They improve ovine fertility, promote luteal function and positively affect ovarian activity in goats (23). They also enhance oocyte cytoplasmic maturation and promote gonadotrophin receptors in cumulus granulosa cells (24). They enhance developmental competence of the oocyte as well as ovarian function and progesterone synthesis (25).

Hormonal secretions are disrupted and disturbed by high temperature (26). (27) reported that high temperature could disrupt the normal status of reproductive hormones in the hypothalamus and ovary, leading to reduced systemic levels and functions, with adverse effect on rabbit performance and productivity. Heat stress alleviators such as niacin due to its role in the regulation of body temperature by vasodilatation (28) are being supplemented in rabbits' diet. The aim of the present study was therefore, to investigate the effect of dietary niacin supplementation to rabbit does' rations on their hormonal response and litter size at birth and at weaning.

Materials and methods

The study was conducted in the Rabbit Unit of the National Animal Production Research Institute (NAPRI), Shika, Zaria, Nigeria, located on latitude 11° and 12°N and between longitude 7° and 8°E with an altitude of 691m above sea level (29). The mean maximum temperature varies from 19^{o}C to 38^{o}C depending on season, while the mean relative humidity during dry and wet season is 21% and 72% respectively. Morning temperature range between 19ºC and 32ºC while afternoon temperature ranged between 20ºC and 40ºC (30). A total of 30 mature crossbred rabbit does aged 18 to 20 weeks, with an average weight of 2.75 Kg were used. The rabbits were weighed and randomly allotted to five dietary groups in a completely randomized design. Each group constituted a treatment and each rabbit within a group was a replicate (6 rabbits/treatment). The rabbits were equally assigned to one of the following levels of niacin (0, 50, 100, 150, 200 mg niacin/kg diet). The experiment lasted for 8 weeks with a 2-week adjustment period.

Hand-mating method was adopted. The does were taken to intact bucks at 8:00 am and 4:00 pm to ensure good courtship and adequate service and returned to their cages after mating. Blood samples were collected from four rabbits per treatment at weekly intervals. The blood samples were collected in the morning (8:00-10:00 am) from the ear veins as described by Feldman *et al.* (31) into sampling bottles without anti-coagulant (heparin).

Hormonal assay was estimated on the pregnant does to determine their hormonal concentrations using the standard protocols of Enzyme-linked immunosorbent assay (ELISA) test kits obtained from Accu-Bind Diagnostics, USA (Monobind Inc., Lake Forest, CA 92630, USA: Progesterone Test System Product Code: 4875-300 and Unconjugated Estriol (u-E3) Test System Product Code: 5025-300). The progesterone AccuLite Microplate CLIA Test System has a sensitivity of 0.208 ng/ml while the Unconjugated Estriol AccuBind Microplate EIA Test System has a sensitivity of 2.9 pg/T. Kindling rate was determined by dividing the number of does that kindled by number of does mated expressed in percentage while litter size of kits was monitored at birth and at weekly intervals up to weaning at 6 weeks after kindling. All data obtained from this study were subjected to the General Linear Model of SAS (32) package and the significant differences in means were separated using pairwise-difference (P-DIFF option of SAS, 32) of the same software.

Results and discussion

The effect of niacin supplementation on hormonal response and litter size of rabbit does is presented in Table 1. Does fed 100, 150 and 200 mg niacin/kg diet had significantly ($P<0.05$) higher oestradiol and progesterone concentrations as well as litter size at birth and at weaning than their counterparts fed 0 mg niacin/kg diet. The concentrations were similar ($P>0.05$) for does fed treatments containing 0 and 50 mg niacin/kg diet. Higher oestradiol and progesterone concentrations observed in does fed 100, 150 and 200 mg/kg diet compared to their counterparts fed the control diet suggest that niacin had ameliorative effect on adverse effect of heat stress which could reduce bio secretion and concentrations of the two hormones in rabbits. Although, heat stress has been reported to inhibit oestradiol and progesterone synthesis and concentrations in breeder cows (13). However, incorporation of vitamins including niacin into feeds could modulate reproductive functions (such as litter size) in rabbits, noting that this could have positive effects on their general biological function/performance (33).

The effect of breeding period on hormonal response of rabbit does is presented in Table 2. The results indicated that oestradiol concentration, one or two weeks before mating was similar but significantly($P<0.05$) higher than the concentration one or two weeks after mating. On the other hand, the reverse was the case with progesterone concentration, one or two weeks after mating was similar but significantly ($P<0.05$) higher than the concentration in two and one week before mating. Higher oestradiol concentration in the two weeks before breeding and the higher progesterone concentration in the two weeks after breeding were observed in the does as expected. (34) and (35) reported that higher concentrations of progesterone and possibly lower concentration of oestradiol are observed during pregnancy than during non-pregnant dioestrus period in many domestic mammals.

The interaction between niacin levels and breeding periods on hormonal response of rabbit does is shown in Figure 1. Oestradiol concentration was similar ($P>0.05$) but significantly ($P<0.05$) higher in does fed 100 and 200 mg niacin/kg diet than does fed 0, 50 and 150 mg niacin/kg diet in the two weeks before mating (Figure 1i). Similarly, progesterone concentration was significantly ($P<0.05$) higher in does fed 150 and 200 mg niacin/kg diet than does fed 0, 50 and 100 mg niacin/kg diet in the two weeks after mating (Figure 1ii). Across all the niacin supplementation levels, higher oestradiol concentration in the two weeks before breeding and higher progesterone concentration in the two weeks after breeding were observed in the does. (36) reported that in rabbits, progesterone levels must be sufficiently higher after fertilization to ensure a uterine environment favourable to the establishment and maintenance of pregnancy while oestradiol concentration must be maintained at a level suitable for normal foetal growth and development. Low concentration of progesterone in pregnant rabbit does may be detrimental to foetal growth and survival (37). The consistently higher oestradiol concentration in the two weeks before breeding observed in does fed diet supplemented with niacin at 100 and 200 mg/kg diet during the first parity suggests that niacin stimulated the production of the hormone from the follicles in the animals. Progesterone levels must be sufficient to ensure a uterine environment favourable to the establishment and maintenance of pregnancy. Therefore, low concentration of progesterone in pregnant rabbit does may be detrimental to foetal growth and survival (38). The higher oestradiol concentration in the two weeks before breeding and the higher progesterone concentration in the two weeks after breeding were obtained in the does as expected during the two parities. (33) and (34) reported that higher concentrations of progesterone and possibly lower concentration of oestradiol are observed during pregnancy than during non-pregnant dioestrus period in many domestic mammals. Progesterone's alterations in its concentration in circulation significantly affects conceptus elongation as well as endometrial gene expression patterns (39). (38) suggested that progesterone levels must be sufficient to ensure a uterine environment favourable to the establishment and maintenance of pregnancy in rabbits; its low concentration in pregnant rabbit does may be detrimental to foetal growth and survival. High level of progesterone indicates that a female animal is not on estrus while its low level indicates that the animal is on estrus, or near estrus (40).

The effect of niacin levels on doe performance, litter size and litter weight of rabbit does during first parity is presented in Table 3. The results indicated that all the litter parameters (litter size and weight) measured significantly ($P<0.05$) increased as the level of niacin supplementation increased. Litter size and weight of does on 100, 150 and 200 mg niacin diet was significantly ($P<0.05$) higher than does on 0 mg/kg niacin diet; does on 0 mg/kg niacin diet had similar ($P>0.05$) size and weight as on 50 mg/kg niacin diet. However, litter weight of does on 50, 100, 150 and 200 ng niacin diet was significantly ($P<0.05$) higher than on 0 mg/kg niacin diet in the fourth week and at weaning. Levels of niacin supplementation did not significantly ($P>0.05$) affect pregnancy and kindling rates. Improved litter size at birth and alive at birth was observed in rabbit does fed dietary niacin supplementation (100, 150 and 200 mg/kg diet), compared to their counterparts fed the control diet. The results may be attributed to the potency of niacin to ameliorate the harmful effect of heat stress and improved follicular growth and development in the does. The vitamin could also be said to enhance the productive and reproductive traits which have resulted in better performance in the animals. Lower litter size at birth/alive at birth may be a consequence of ovaries carrying a pre-ovulatory follicle due to increased negative impact of heat stress in rabbit does under high ambient temperature (41). Heavier litter weight was observed in rabbit does fed dietary niacin supplementation (100, 150 and

200 mg/kg diet) compared to their counterparts fed the control diet in the first, second, third and fifth week of lactation. These observations suggest that niacin probably ensured adequate milk production in the dam during these early weeks of life. Decrease milk intake could cause a decrease in the concentration of growth regulating factors, such as insulin-like growth factors (42) in rabbit kits, which may likely results in impaired normal growth and development of the kits. This observation could be traced to their improved birth weight (400.00, 530.10, 490.00 vs. 320.15 g) due to niacin supplementation. (43) suggested that birth weight of rabbit kits was positively correlated with daily/weekly weight gain.

The effect of niacin levels on doe and kit mortality of rabbit does during first parity is presented in Table 4. Stillbirth, kit mortality in the first week, at weaning and total kit mortality significantly ($P<0.05$) decreased as the level of niacin supplementation increased. Does on 0 mg niacin diet had significantly ($P<0.05$) higher stillbirth, kit mortality in the first week, at weaning and total kit mortality than on 50, 100, 150 and 200 mg niacin diet. Doe mortality, kit mortality from the second to the fifth week were not significantly ($P>0.05$) affected by the levels of niacin supplementation. Lower stillbirth was observed in rabbit does fed dietary niacin supplementation compared to does fed the control diet in this study. This result indicates that niacin apparently improved embryonic development, prevented birth defect and enhanced adequate supply of oxygen and nutrients crossing the placenta from the does to the developing embryos/foetuses. The mechanism by which heat stress decreases litter size alive at birth or increases stillbirth in rabbit kits is not fully understood. However, abnormal follicle and impaired *corpus luteum* development, low quality oocytes and high embryo mortality in rabbit does under heat stress induced by elevated temperature could be considered the leading factors (43). Foetal growth/embryonic development depends exclusively on an adequate supply of oxygen and nutrients crossing the placenta from the rabbit does to the fetus/embryo (37, 44). Lower kit mortality in the first week of lactation and total kit mortality was observed in rabbit does fed niacin supplemented diet compared to their counterparts fed the control diet. The current findings suggest that niacin ameliorated the adverse effect of heat stress in the kits. Niacin could also possibly enhance the physiological and other vital processes associated with improved immune status/immunocompetence and survival of rabbit kits. Effect of heat stress induced by high temperatures on the reproductive performance and kit's survival rate of rabbit does has been documented (45; 46). Lower kit mortality at weaning was observed in rabbit does fed dietary niacin supplementation (50, 150 and 200 mg/kg diet). This result suggests that niacin sufficiently alleviate some causes of post-natal and pre-weaning kit mortality including excessive ROS formation, diseases caused by environmental or increased physiological stress. Several previous researchers had demonstrated that daily intake of niacin up to 6.0 g or more was administered for the prevention of over-production of ROS, which could lead to high mortality in humans (47; 48).

Conclusion and application

1. It is concluded that dietary niacin supplementation (100, 150 and 200 mg niacin/kg diets) used in the present study in rabbit does had an ameliorative effect on the hormonal responses of the rabbit does.

2. Further investigation is suggested on the response of rabbits to niacin supplementation in combination with other exogenous antioxidants.

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Table 1: Effect of niacin supplementation on hormonal response and litter size of rabbit does

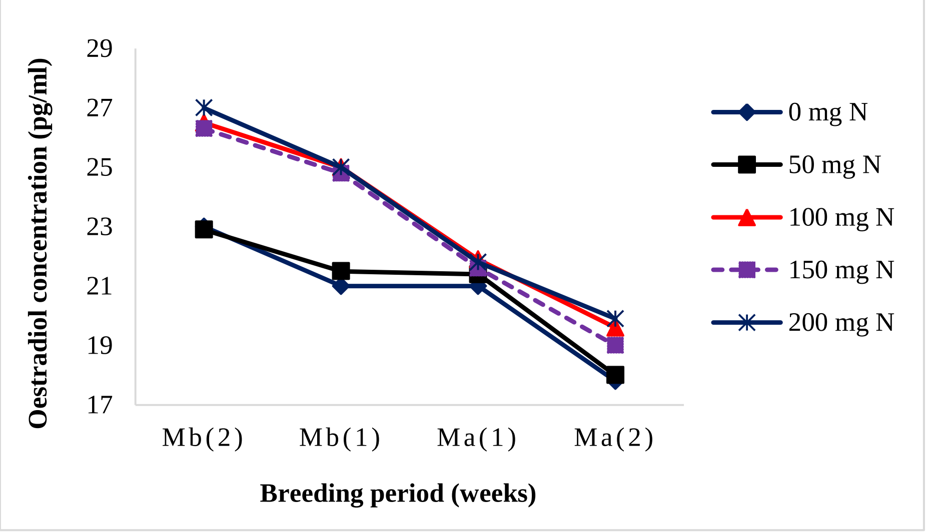
Hormones	Niacin levels (mg/kg feed) 0	50	100	150	200	P value
	(LSMeans ± SE)(n=6)					
Oestradiol (pg/ml)	24.84±0.31[c]	25.43±0.31[bc]	26.02±0.31[ab]	26.25±0.31[a]	26.40±0.40[a]	0.050
Progesterone (ng/ml)	7.63±0.13[c]	7.68±0.13[c]	8.18±0.13[b]	8.76±0.13[a]	8.90±0.41[a]	0.045
Kindling rate (%):	100.00±10.09	100.00±10.09	100.00±10.09	100.00±10.09	100.00±10.09	0.209
Litter size at birth	6.20±0.62[c]	6.50±0.62[bc]	7.50±0.62[ab]	8.50±0.62[a]	7.90±0.62[a]	0.048
Litter size at weaning	5.00±0.57[c]	5.75±0.59[bc]	6.80±0.57[a]	7.45±0.58[a]	7.10±0.59[a]	0.012
Stillbirth	3.23±0.28[a]	1.05±0.28[b]	0.67±0.28[b]	1.18±0.31[b]	0.63±0.28[b]	0.017

[abcd]: Means with different superscripts in the same row are significantly (P<0.05) different

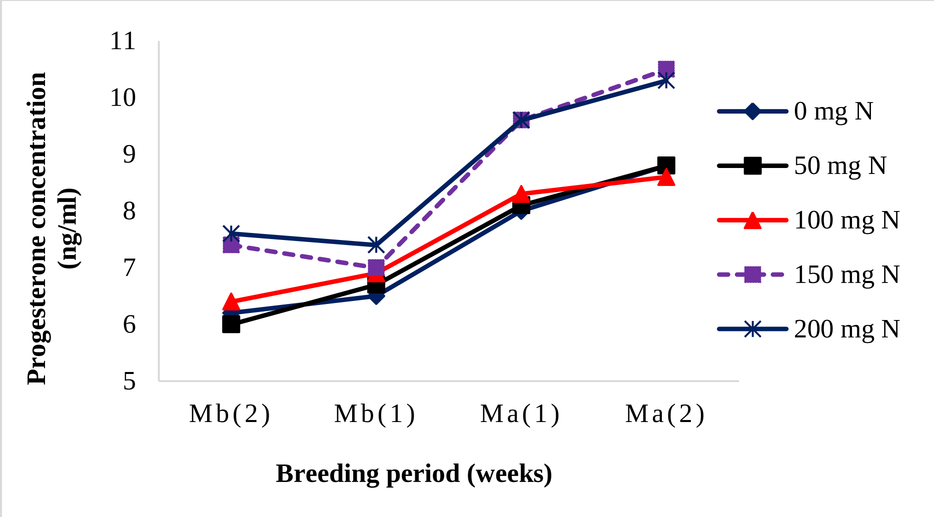
Table 2: Effect of breeding periods on hormonal response of rabbit does

Hormones	Breeding Period (weeks) Mb (2)	Mb (1)	Ma (1)	Ma (2)	P value
	(LSMeans ± SE)(n=6)				
Oestradiol Concentration (pg/ml)	26.25±0.70[a]	26.07±0.64[a]	23.95±0.64[b]	22.80±0.64[b]	0.001
Progesterone Concentration (ng/ml)	6.93±0.33[b]	7.41±0.33[b]	8.75±0.33[a]	8.79±0.36[a]	0.001

[ab]Means with different superscripts in the same row are significantly (P<0.05) different, Mb(2)=Two weeks before mating, Mb(1)=One week before mating, Ma(1)=One week after mating and Ma(2)=Two weeks after mating



i) Oestradiol concentration



ii) Progesterone concentration

Figure 1: Interaction between niacin levels and breeding periods on oestradiol (SEM=0.36, P=0.04) and progesterone concentrations (SEM=0.84, P=0.03) in rabbit does before mating and during pregnancy. Values expressed as mean and SEM (vertical bars)(n=6), N=Niacin, Mb(2)=Two weeks before mating, Mb(1)=One week before mating, Ma(1)=One week after mating and Ma(2)=Two weeks after mating

Table 3: Effect of niacin levels on doe performance, litter size and litter weight of rabbit does during first parity

Parameters	Niacin levels (mg/kg)					P value
	0	50	100	150	200	
Pregnancy rate (%)	100.00±10.01	100.00±10.01	100.00±10.01	100.00±10.01	100.00±10.01	0.400
Kindling rate (%):	100.00±10.09	100.00±10.09	100.00±10.09	100.00±10.09	100.00±10.09	0.209
Litter size:						
At birth	6.20±0.62^{c}	6.50±0.62^{bc}	7.50±0.62^{ab}	8.50±0.62^{a}	7.90±0.62^{a}	0.048
Alive at birth	6.00±0.66^{c}	6.40±0.66^{bc}	7.45±0.66^{ab}	8.40±0.66^{a}	7.85±0.66^{a}	0.035
First week	5.85±0.75^{c}	6.35±0.75^{bc}	7.40±0.75^{ab}	8.35±0.75^{a}	7.75±0.75^{ab}	0.050
Second week	5.70±0.70^{c}	6.30±0.70^{bc}	7.25±0.70^{ab}	8.15±0.70^{a}	7.60±0.70^{ab}	0.026
Third week	5.48±0.45^{b}	6.30±0.45^{b}	7.25±0.45^{a}	7.95±0.48^{a}	7.60±0.48^{a}	0.037
Fourth week	5.55±0.72^{c}	5.95±0.70^{bc}	7.10±0.70^{ab}	7.70±0.72^{a}	7.45±0.72^{a}	0.019
Fifth week	5.35±0.71^{c}	5.95±0.71^{bc}	6.95±0.71^{ab}	7.60±0.71^{a}	7.30±0.71^{ab}	0.040
At weaning	5.00±0.57^{c}	5.75±0.59^{bc}	6.80±0.57^{a}	7.45±0.58^{a}	7.10±0.59^{a}	0.012
Litter weight (g):						
At birth	320.15±28.50^{c}	350.05±28.25^{bc}	400.00±28.50^{b}	530.10±28.22^{a}	490.00±28.25^{a}	0.050
Alive at birth	300.00±27.11^{c}	320.00±27.11^{c}	385.25±27.11^{b}	522.00±27.11^{a}	450.00±27.11^{a}	0.022
First week	590.00±40.00^{b}	610.50±40.00^{b}	700.20±40.00^{a}	760.00±40.00^{a}	730.00±40.00^{a}	0.048
Second week	800.50±60.88^{c}	840.25±60.88^{bc}	925.20±60.88^{ab}	990.90±60.88^{a}	960.05±60.88^{ab}	0.010
Third week	1035.00±75.55^{c}	1080.50±75.53^{c}	1450.00±75.54^{b}	1800.00±75.53^{a}	1650.00±75.55^{a}	0.009
Fourth week	1400.00±88.95^{e}	1690.50±88.95^{d}	1950.00±88.95^{c}	2500.50±88.95^{a}	2300.50±88.95^{b}	0.037
Fifth week	2650.50±92.12^{d}	2700.00±92.12^{d}	3750.20±92.12^{c}	4150.40±92.12^{a}	3950.60±92.12^{b}	0.016
At weaning	3950.00±96.70^{d}	4250.60±96.70^{c}	5270.10±96.70^{b}	5890.00±96.70^{a}	5750.05±96.70^{a}	0.031

^{abcde}: Means with different superscripts in the same row are significantly (P<0.05) different

Table 4: Effect of niacin levels on doe and kit mortality of rabbit does during first parity

Parameters	Niacin levels (mg/kg)					P value
	0	50	100	150	200	
Doe mortality (%)	0.00±1.33	0.00±0.33	0.00±0.33	0.00±0.33	0.00±0.33	0.198
Kit mortality (%):						
Stillbirth	3.23±0.28[a]	1.05±0.28[b]	0.67±0.28[b]	1.18±0.31[b]	0.63±0.28[b]	0.017
First week	2.50±0.62[a]	0.78±0.62[b]	0.67±0.62[b]	0.60±0.65[b]	0.64±0.62[b]	0.045
Second week	2.56±1.51	1.56±1.51	2.03±1.51	2.40±1.85	2.56±1.51	0.242
Third week	0.00±1.79	0.00±1.79	0.00±1.79	2.45±1.96	0.00±1.79	0.257
Fourth week	2.63±2.23	5.56±2.23	2.07±2.23	3.14±2.44	1.97±2.23	0.421
Fifth week	3.60±2.37	0.00±2.37	2.11±2.37	1.30±2.60	2.01±2.37	0.556
At weaning	6.54±1.99[a]	3.36±1.99[b]	2.21±1.99[b]	1.97±2.18[b]	2.74±1.99[b]	0.034
Total	19.35±2.87[a]	11.54±2.87[b]	10.67±2.87[b]	12.35±2.90[b]	10.13±2.87[b]	0.018

[abc]: Means with different superscripts in the same row are significantly (P<0.05) different

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