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Abstract

Stress management is a significant factor in industrial livestock farms. Farm managers have always been trying to decrease stress in their farm animals and overcome its adverse effects. In this study, anti-stress effects of Stress-Pack® feed additive, manufactured by BIOCHEM GmbH., Germany was investigated in an industrial cow farm at the time of foot and mouth disease (FMD) vaccination, a stress inducing factor. Cows were divided in control and treatment groups (received 12 g or 24 g Stress-Pack®, 2 days before and 1 day after vaccination) and evaluated for hematological changes, milk yield, pregnancy rate and anaphylactic shock before and after vaccination.

Results showed that after vaccination, in treatment group that received 12 g Stress-Pack®, not only no reduction in milk yield was seen but also significant increase in milk production happened.

Introduction

Stress is a dysregulation in homeostasis mechanisms keeping the normal physiological function of the animal/birds. Generally the term "Stress" is used to describe the detrimental effects of variety of factors on the health and performance under the stress conditions. Stress leads to redistribution of body resources including energy and protein at the cost of decreased growth, reproduction and health (Beck, 1991; Brake, 1987; Gross and Siegel, 1987). Control of stress is one of the significant managing factors in poultry and livestock farms. If farmers ignore this factor they will face with direct and indirect financial loss. Furthermore, developing more accurate measures of stress will enable producers to monitor changes in animal husbandry or production (Chen, Y., *et al.* 2015). Epidemiological evidence has linked a wide variety of stressors, especially transportation, noise pollution, overcrowding, extreme heat and cold weather, diseases, vaccination, reactions to adjuvant of vaccines or allergens, etc.

Foot-and-mouth disease (FMD) is an economically important disease of cloven-hoofed farm animals and is probably the most contagious disease known. FMD is still a major problem and one of the most difficult to control in the Middle East and other endemic areas. Intensive annual vaccination campaigns contribute to controlling the disease, reducing the number of outbreaks, and preventing the spread of FMD within the country and to neighboring countries (Yeruham, I., *et. al*, 2001).

Vaccination program is performed in dairy cow farms according to a strategic program in Iran. In this program vaccination is performed against brucellosis, Foot and Mouth Disease (FMD), Anthrax (some regions), Lumpy Skin disease, etc. Based on previous studies, subsequent to vaccination with some vaccines like FMD, post-vaccination allergic reactions like urticaria, exudative and necrotic dermatitis, along with edema and vesicles on the teats, anaphylactic shock and even death are described and reduction in milk production for 2 to 5 consecutive days and decline in pregnancy rate have been reported (Yeruham I, *et. al*, 2001). In a study in 1997 in Canada, it was reported that vaccination with Herpes Virus showed 1.4 L reduction in milk production (Bosch JC, et al. 1997). In another research, 7% decline in milk production was reported subsequent to *E. coli J5* vaccination (Musser JM, et al., 1996).

Quantifying responses to experimental or natural stressors is an important first step in determining the potential effects of acute or chronic stressors. The measurement of levels of adrenal glucocorticoid hormones, such as cortisol or corticosterone, in plasma has proven to be an invaluable tool. As with all methods, however, there are drawbacks associated with it. For example, levels of plasma corticosterone rise quickly immediately following stress (Davis A. K. et.al, 2008).

Furthermore, the use of haematological parameters such as relative white blood cell (WBC) counts made from blood smears is another method in order to quantify stress in animals. This approach may represent an alternate method for measuring corticosterone. because increase in glucocorticoid hormones cause characteristic changes in the leukocyte component of the vertebrate immune system that can be quantified and related to hormone levels. Specifically, the changes brought on by stress or glucocorticoid treatment are increases in numbers of neutrophils (neutrophilia) and decreases in lymphocyte numbers (lymphopenia or lymphocytopenia). Moreover, since numbers of neutrophils and lymphocytes are affected by stress in opposite directions, researchers have often considered the ratio of one to the other, that is, the relative proportion of neutrophils to lymphocytes (hereafter, 'N: L' ratio) in mammals and amphibians, and heterophils to lymphocytes (hereafter, 'H: L' ratio) in birds and reptiles, as a composite measure of the stress response (Davis A. K. et.al, 2008).

Cows are subjected to frequent stress factors, and therefore it is important to have an effective management program to minimize stress effects on the performance and health condition of the cows. Effective management of stress, however, depends on the ability to identify and quantify the effects of various stressors and determine if individual or combined stressors have distinct biological effects. Furthermore, it is critical to determine the duration of stress-induced biological effects if we are to understand how stress alters animal production and disease susceptibility and finally reduce adverse effects of stress by controlling it.
The objectives of this study were investigating effects of Stress-Pack® feed additive (Biochem GmbH., Germany) on reducing stress adverse effects and its effects on milk production and pregnancy rate at the time of stress.

Materials and Methods

The study was done in a dairy cattle farm, comprised of 6000 cows divided in 2 herds, located in Javad-Abad region of Pishva, Varamin, Iran. Under-study cows belonged to the herd with population of 3050 cows (1250 lactating cow). The dairy herd was maintained under an intensive management system and had a mean herd milk yield of 40 kg per cow per day. The average of pregnancy rate was 40.5% at the time of vaccination.

Under-study Population:
In order to investigate effects of stress due to FMD vaccination on milk yield, 737 dairy cows were evaluated in 5 yards as 5 groups: group 'A' as control (first-lactation cows); group 'B' as treatment (first-lactation cows that received 12 g Stress-Pack®/head/day); group 'C' as control (high-producing dairy cows/head/day); group 'D' as treatment (high-producing dairy cows that received 12 g Stress-Pack®/head/day); group 'E' as treatment (high-producing dairy cows that received 24 g Stress-Pack®/head/day) (table 1).

Table 1: under-study groups

Groups	Description	size
A	Control (First-lactation cows)	132
B	First-lactation cows (12 g Stress-Pack®)	105
C	control (high-producing dairy cows)	252
D	high-producing dairy cows (12 g Stress-Pack®)	134
E	high-producing dairy cows (24 g Stress-Pack®)	114

Vaccination

All cows in 3 groups were vaccinated with the inactivated FMD vaccine (produced by Razi Vaccine and Serum Research Institute, Iran) containing several serotypes: O pan, O 2010, A05IR and Asia 1 and adjuvants: aluminium hydroxide gel and saponin. After vaccination, all cows in study groups were clinically examined for anaphylactic shock symptoms.

Treating with Stress-Pack® Additive

All cows in groups B, D and E received 12, 12 and 24 g Stress-Pack® per day per cow in feed for a 3-day period (2 days prior and 1 day post vaccination).

Blood Sampling

96 blood samples collected from control & treated groups (high-producing dairy cows) prior and post vaccination (1 day after vaccination). Blood samples collected with veinoject via tail vein. All blood samples were analyzed for CBC test and their white blood cell differential counts were reported.

Milk Yield Recording

Daily milk yields were recorded in the day before and after vaccination. Stress-Pack® was measured and added to concentrate for 3-day consumption.

Pregnancy Rate calculation

Pregnancy Rate is a more accurate and useful measurement of total herd reproductive performance. This indicates the percentage of cows in a herd that become pregnant every 21-day period after the voluntary waiting period.

$$\text{Heat Detection Rate} = \frac{\text{\# of cows inseminated over 21 days}}{\text{\# of cows elegible to be bred over 21 days}}$$

$$\text{Conception Rate} = \frac{\text{\# of cows pregnant}}{\text{\# of cows inseminated}}$$

$$\text{Pregnancy Rate} = \text{Heat Detection Rate} \times \text{Conception Rate}$$

Statistical Analysis

All data were statistically analyzed by one-way analysis of variance (ANOVA) and paired t-test.

RESULTS

The results for blood samples analysis and milk yield records are presented in table 2 and table 3, respectively.

Table 2: white blood cell differential count in test groups: control and treatments (average ± standard deviation)

Groups	Neutrophil %	Lymphocyte %	Neut/ Lymph	Eosinophil %	Monocyte %
Control	43.1± 13.9	51.6 ± 14.8	0.83	0.53±1	1.47±4.1
Treatment 1	37 ± 12	12.7 ± 57	0.64	0.4± 1.1	2.4 ± 4.5
Treatment 2	39.8 ± 12.6	13 ± 53	0.75	1.4 ± 1.8	1.8 ± 4.9

In normal conditions, Neutrophil to Lymphocyte Ratio in cow is around 0.53-0.65.
Cows with high milk yield that received 12 and 24 gram Stress-Pack® showed 0.64 and 0.75 N: L ratio, respectively. The results show that N/L in the treatment 1 (receiving 12 g stress pack per cow) is more near to normal condition and is less effected by stress in comparison to other under-study groups. In contrast, in control group the N: L ratio was significantly higher than treatment groups. These results demonstrate the effects of stress induced by vaccination in cows that didn't receive Stress-Pack®.

Milk Yield

Average of milk production decreased in control groups following the FMD vaccination but it was very low (3% reduction), "most probably due to high-quality management system in the farm". In treated groups B & E not only any reduction was reported but also slight increase was seen in these yards (3 %) but they weren't statistically significant. In group D which received 12 g Stress-Pack®, a significant difference was seen in milk yield before and after vaccination ($P<0.05$) that can be due to effects of Stress-Pack® Ingredients.

Pregnancy Rate

Significance of pregnancy rate parameter in a dairy farm on one hand and the effects of stress on this parameter on the other hand brought it under consideration and its' related data were analyzed and came under discussion. This study was done in winter, a season that average pregnancy rate is in highest level in the year. The results demonstrated that, average pregnancy rate in group A and group B were 41.2 and 47.3, respectively. In group C, D and E, average pregnancy rates were 38.85, 44.2 and 46.1, respectively (table 3). In conclusion, cows that received Stress-Pack® feed additive for 3 days had higher pregnancy rate in comparison to control groups.

Table 3: Average of milk production in test groups before and after vaccination (average ± standard deviation)

Group Name	Description	population	Average calving rate	Average of milk yield before vaccination	Average of milk production after vaccination	P Value of changes in milk yield before and after vaccination	Average pregnancy rate
A	Control (First-lactation cows)	132	1	41	39.8	-	41.2
B	First-lactation cows (12 g Stress-Pack®)	105	1	40.9	41.53	0.098	47.3
C	control (high-producing dairy cows)	252	2.5	49.4	47.7	-	38.85
D	high-producing dairy cows (12 g Stress-Pack®)	134	2.8	50.7	54.2	0.000018*	44.2
E	high-producing dairy cows (24 g Stress-Pack®)	114	2.6	48.8	50.4	0.085	46.1

* Significant difference between the control and treated group

DISCUSSION

For both animals and humans, stress can be conceptualized as the exposure to environmental events and conditions that perturb psychological and/or physiological homeostasis (Sheehy, N., *et. al,* 1997). In recent years, the psychological or physical effects of stress hormones have been investigated in several human researches (Duff, G.C., *et. al.,* 2007).

In farm animals, most of stress studies have been done on poultry. In first studies, layers went under investigation and then broilers. In cattle, the effects of environment on milk yield had always been under consideration. Transportation may, however, be comprised of many different stressors, including feed and water deprivation, thermal, restraint, and social re-organization during and after transfer to a new environment. Furthermore, commingling animals from multiple sources during this process may increase exposure to viral and bacterial agents (Duff, G.C., *et. al.,* 2007). Hence, the impact of stressors on cow welfare and production capacity should be evaluated in order to recommend solutions to overcome stress and maintain the normal production capacity of herd.

Recent studies showed that, from the perspective of domestic animal production, physiological changes due to stress may manifest as altered behavior, decreased immune protection that impacts disease susceptibility, or altered metabolism that impacts either growth, production, or a combination of these responses. These changes in animal production may be very difficult as many of these manifestations may occur at a subclinical level. Being able to measure the effects of stress on immunity and metabolism at a molecular level is critical if we are to engage in an informed discussion regarding the impact of a specific stressor, or combination of stressors, on animal health, well-being, and production (Chen, Y., *et al.* 2015).

The leukocyte approach offers certain advantages over direct glucocorticoid measurement in that it does not require prohibitively rapid sampling and is relatively inexpensive (Davis A. K. *et.al*, 2008). The rapid and pulsatile releases of corticosteroids from the adrenal cortex make this a very dynamic response. To minimize this problem, blood samples are generally collected within minutes of an animal being exposed to the stressor (Mormede, P., *et. al,* 2007). Thus, it is critical that both the method of sample collection and the time of samples collection be considered when designing stress experiments and interpreting data. Cortisol concentrations in cattle have also been measured in urine, saliva, hair, feces, and milk (Davis A. K. et.al, 2008).

In response to glucocorticoids like cortisol or corticostrone, circulating lymphocytes adhere to the endothelial cells that line the walls of blood vessels, and subsequently undergo transmigration from circulation into other tissues, for example lymph nodes, spleen, bone marrow and skin, where they are sequestered (Cohen 1972; Fauci 1975; Dhabhar 2002). This exodus of lymphocytes from the blood causes a significant reduction in their circulating numbers. In contrast, glucocorticoids also stimulate an influx of neutrophils into the blood from bone marrow and attenuate the egress of neutrophils from the blood to other compartments (Bishop *et al.* 1968). Accordingly, studies showed that N: L ratio is considered to be a reliable indicator of stress, since leucocyte changes in response to stress are less variable and more enduring than those resulting from the cortisol/corticosterone response.

Since N: L ratio is one of the recommended quantitative methods for diagnosis stress in animals in several published papers, the results indicated that Stress Pack can decrease stress in cows in stressful conditions like vaccination.

There are additives or supplements that can alleviate stress cycle by effect on stress hormone (like cortisol) release and providing some minerals or vitamins that are essential for metabolic or immunological functions. Accordingly, utilizing them in stressful conditions is really recommended. Stress-Pack® ingredients can control stress in cows by reducing cortisol release, improving metabolic cycle, strengthening the immune system and calming animal.

In conclusion this study showed that Stress Pack can improve the drop in milk yield which is one of the adverse effects of stress due to vaccination in dairy cows. Adding 12 g Stress-Pack® per cow to feed, 2 days before and 1 days after vaccination, can reduce the adverse effects of stress due to vaccination and will increase pregnancy rate in dairy cows.

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