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Research Article

IMPROVEMENT OF THE BIOCHEMICAL AND METABOLIC BIOMARKERS IN RESPONSE TO THE THERAPEUTIC MANAGEMENT IN KETOTIC DAIRY COWS

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ABSTRACT: The aim of this study was to investigate the changes in biochemical and metabolic biomarkers in urine, milk and blood of ketotic dairy cows in and around Bhubaneswar, Odisha, India, before and after treatment. Thirty of 100 ketotic cows identified from a population of 1014 cows were equally divided into three groups of 10 animals each while group IV selected from the population under investigation was treated as control. Following treatment in group III, the ALT, AST, ALP and LDH levels observed in ketotic animals at pre-treatment were decreased maximum at post-treatment. It can be concluded that the treatment package comprising of Dextrose (25%) intravenously, sodium propionate (orally), liver extract with vitamin B complex injection intramuscularly, dexamethasone injection intravenously and insulin injection subcutaneously practiced in group III was the most efficacious and superior to group I and II in the treatment of bovine ketosis for bringing the biochemical profiles to normal. The therapeutic regimen of group III exhibited better performance than other groups might be due to the synergistic therapeutic effect of insulin in glucose metabolism.

Key words: Ketosis, Dairy cows, Treatment, Biomarkers.

INTRODUCTION

Ketosis, a major metabolic disorder in dairy cows during the early lactation period, inflicts considerable economic loss in dairy farming due to amplified vulnerability to disease and decreased reproductive performance and fertility in dairy cows. Recent developments suggest that ketosis is a multi-factorial disorder of energy metabolism. If energy homoeostasis is not controlled, the negative energy leads to hypoglycemia (Zhang *et al*. 2009, Radostits *et al*. 2010). Almost all high-producing dairy cows are in negative energy balance in early lactation, because energy requirements surpass their capacity to consume adequate feed. The drop in blood glucose levels in early lactation prompts ketosis causing a high degree of mobilization of non-esterified fatty acids (NEFA) which are, then, oxidized by the liver, and results in the production of ketone bodies such as acetone, acetoacetate, and β- hydroxybutyrate (Xu *et al*. 2016).

Identification and determination of a cow's hemogram soon after parturition, during the lactation period and pregnancy to calving time is considered as the main method of improvement in the dairy herd output and consequently for maintaining the milk production (Kupczynski *et al*. 2011, Djokovic *et al*. 2013). Dairy cows are exposed to numerous hematological and biochemical changes, particularly in late gestation and early lactation. Various factors influence a metabolic profile in animals. The reliable indicators of health status of dairy cows in peripartum period are hematological, metabolic and biochemical parameters. A transitional period in dairy cows is followed by physiological, metabolic and nutritional changes and the changes, thus, built up have a great influence on lactation performance, reproductive disorders, subclinical and clinical postpartum ailments and, thus significantly affecting profitability (Block 2010, Todorovic and Davidovic 2012).

During lactation period, concentrations of haematological parameters and their interrelationships were investigated in dairy cows to determine the variations among parameters which could be most reliable and useful

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indices for understanding milk yield improvement (Nozad *et al*. 2014). Moreover, blood glucose levels, total triglycerides, and aspartate aminotransferase (AST) can also be analysed to monitor ketosis-related complications (Ilves *et al*. 2012). Although investigations on bovine ketosis have been carried out in Odisha by Biswal (1993), Jena (2000) and Panda (2003), further study still remains unsolved to find out the remedial measures through cost effective and efficacious therapeutic regimen and awareness of dairymen. Thus, the objective of this research was the therapeutic management of biochemical and metabolic biomarkers in ketotic dairy cows which is a step forward towards the improvement of the health and milk production in dairy herds.

MATERIALS AND METHODS

The present study was conducted in the Department of Veterinary Medicine, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha State, India. Ketotic dairy cows (n=100) screened through Rothera's test were selected randomly from a population of 1014 crossbred Jersey, Holstein Friesian and indigenous ketotic cows. Thirty of 100 ketotic cows were randomly selected and equally divided into three groups. Group I to III under therapeutic trial received medicines and ten animals were selected and treated as control (group IV). Studies of metabolic such as ketone bodies and biochemical parameters namely, insulin, glucose, calcium, magnesium, cholesterol, triglycerides, total protein, ALT, AST, ALP and LDH were carried out in group I, II and III at pre-treatment and on 3rd day and 7th day of post-treatment. The biochemical parameters were also estimated in group IV at pre-treatment and on 3rd day and 7th day without treatment. Daily milk yield was recorded to know the status of production and, the milk yield in pre-treatment and post-treatment was observed during therapeutic management of ketotic dairy cows.

Collection of blood samples

Blood sample (3 ml) collected from each animal by jugular venipuncture in a clean and dry vial containing fluoride oxalate was transferred to the laboratory for estimation of plasma glucose (Varley *et al.* 1980). Similarly, blood (10 ml) from each cow was again collected to separate serum and stored at –20 °C for other biochemical parameters. Serum samples were collected on 3rd day and 7th day of post-treatment from each treatment group. The estimation of ketone bodies (acetone with acetoacetate) was done as per the method described by Henry (1969).

Estimation of serum insulin

The estimation of serum insulin was carried out by the electro chemiluminescence immuno assay (ECLIA, M/s Roche Diagnostics, Elecsys). Results were determined via a calibration curve which is instrument generated by 2-point calibration and a master curve provided via the reagent barcode.

Estimation of plasma glucose

The plasma glucose (GOD/POD method - reagent kit (Ecoline, supplied by M/S E. Merck (India) Limited, Mumbai) by Colorimetric method; serum calcium (Arsenazo III) and magnesium (Calmagite-EGTA) were estimated, respectively, on employing the reagent kit (Lab kit, Chemelex, S.A. Pol. Ind. Can Castells) through Lambda 25 UV-VIS Spectrophotometer (M/S Perkin Elmer Pvt. Ltd, USA).

Estimation of biochemical parameters

The serum ALT, AST (IFCC method), ALP, LDH (DGKC method) cholesterol (CHODPAP method), triglyceride, and total protein (Biuret method) were estimated as specified with the reagent kit (Ecoline) supplied by M/s Merck Limited, Mumbai through Lambda 25 UV-VIS Spectrophotometer manufactured by M/s Perkin Elmer Pvt. Ltd. USA.

The ketotic dairy-cows in group I were administered with Dextrose (25 %) injectable solution (M/s Merind Wockhardt Ltd.) intravenously @ 0.5 gm/kg of body weight at 12 hr intervals for 7 days. Sodium propionate (M/s LobaChemie Ltd.) was administered orally @ 200 gm per animal daily for 7 days and 10 ml of Neohepatex (Liver extract with vitamins) injection (M/s Biological Evans Ltd.) per cow intramuscularly daily for 3 days. The group II animals received the treatment as group I along with Decdan (Dexamethasone) injection (M/s Merind Wockhardt Ltd.) @ 20 mg/animal intravenously at 12 hr intervals for 1st day followed by 16 mg/animal at 12 hr interval for next two days. The ketotic animals clubbed in the treatment group III received the treatment as in group II together with insulin (M/s Abbott Pharmaceuticals Ltd.) injection @ 0.5 IU/kg body weight once only during the administration of Dextrose (25%) therapy.

The ketotic index of each animal under investigation was meticulously examined for assessment of the degree of severity of the disease at pre-treatment and post-treatment stages. The blood metabolites were determined to know the degree of pathogenicity and special attention was given for estimation of ketone bodies in urine, milk and blood. Clinical signs like anorexia, selective appetite, refusal of concentrate, reduced body condition, acetone like smell emitted from breath and milk, declination to move and graze, excitement, bellowing, head pressing against the stanchion or wall or any object, stretching of the tie-rope and leaning forward, licking of the body,

Table 1. Therapeutic effect of different medicines on the biochemical parameters in ketotic dairy cows.

Parameters	Group I (n=10)			Group II (n=10)			Group III (n=10)			Group IV (n=10)		
	Pre-treatment	Post-treatment		Pre-treatment	Pre-treatment		Pre-treatment	Post-treatment		Pre-treatment	Without treatment	
		3rd day	7thday		3rd day	7thday		3rd day	7thday		3rd day	7thday
Insulin µIU/L	3.38± 0.83	10.2± 1.13	13.62± 1.43*	3.36± 0.94	10.46± 1.16	13.73± 2.14*	3.39± 0.73	10.92± 1.03*	14.04± 1.97*	3.36± 0.43	3.44± 1.01	3.41± 0.86
Glucose mmol/L	1.84± 0.09	2.13± 0.08	2.55± 0.07	1.84± 0.08	2.23± 0.10	2.65± 0.12*	1.83± 0.09	2.46± 0.14	2.80± 0.18*	1.83± 0.22	1.82± 0.09	1.81± 0.07
Calcium mmol/L	1.85± 0.08	2.09± 0.07	2.17± 0.12	1.85± 0.09	2.18± 0.08	2.24± 0.14	1.84± 0.13	2.27± 0.24*	2.32± 0.18*	1.86± 0.17	1.84± 0.16	1.84± 0.15
Magnesium mmol/L	0.76± 0.06	0.83± 0.041	0.98± 0.009	0.76± 0.010	0.84± 0.021	0.93± 0.011	0.76± 0.009	0.85± 0.010	0.95± 0.008*	0.76± 0.08	0.76± 0.010	0.76± 0.19
Cholesterol mmol/L	4.53± 0.08	4.56± 0.06	4.67± 0.09	4.47± 0.07	4.57± 0.04	4.69± 0.08	4.39± 0.07	4.58± 0.06	4.70± 0.09	4.68± 0.04	4.76± 0.08	4.80± 0.06
Triglycerides mmol/L	0.16± 0.002	0.15± 0.002	0.15± 0.002	0.16± 0.018	0.15± 0.001	0.15± 0.001	0.13± 0.003	0.15± 0.008	0.18± 0.006	0.16± 0.002	0.16± 0.007	0.16± 0.003
Total protein gm/L	46.99± 2.55	64.1± 3.54	67.63± 1.50	50.82± 3.29	61.24± 2.29	63.02± 2.29	56.05± 4.32	68.37± 3.29	70.97± 2.42*	50.77± 2.56	48.00± 3.54	45.20± 2.93

Glucose and cholesterol were estimated in plasma while other biochemical parameters in serum.
*Superscripts within the columns differ significantly ($p < 0.05$).

incardinated gait and nature of faeces were observed during sampling and treated accordingly. Data were analyzed statistically using independent Students' t - test and significance difference ($p<0.05$) with respect to pre- and post-treatment was calculated (Snedecor and Cochran, 1994).

RESULTS AND DISCUSSION

The present investigation on bovine ketosis succeeded for the first time in the milkshed areas of Odisha to record the prevalence of ketosis as 36.73% (Panda 2003, Oetzel 2004). The prevalence for clinical ketosis and sub clinical ketosis were found to be 27.17% and 9.56%, respectively (Biswal *et al*. 2016). The crossbred cows most often in milk shed areas of Odisha are subject to the predisposing factors of ketosis during lactation. Hence, the purpose of the present investigation was sustained with the holistic approach to bovine ketosis for the fulfillment of the farmers' need by and large.

Metabolic profile of the control cows

The ketone bodies (acetone+acetoacetate) estimated through quantitative method in urine, milk and blood were found to be 1.55±0.015 mg/dl, 1.05±0.006 mg/dl and 1.31±0.014 mg/dl, respectively, in group IV. The colour indices in qualitative estimation of urine and milk varied identically from '+++' to '++++' through Rothara's test for urine and Ross test for milk in all treatment groups. The acetone and acetoacetate estimated for ketone bodies in blood, urine and milk of ketotic cows were in line as documented by Radostits *et al*. (2010). The principal reason of the estimation of ketone bodies in ketotic animals was to know the degree of pathogenicity in ketosis and the impact of ketone bodies on the physiological functions of the body. The acetoacetate and â-hydroxybutyrate concentrations in bovine blood increased when the glucose concentration decreased (Kronfeld and Emery 1970). The milk level of ketone bodies estimated in group III was 1.26 ± 0.09 is in line with Sarode *et al*. (1981) and Vaidya (2002), however, the blood ketone bodies (5.19±1.02 mg/dl) and urine ketone bodies (6.80±1.84 mg/dl) estimated by Baishya *et al*. (2002) were not in agreement with the present findings.

The qualitative estimation of urine and milk in group III revealed the color indices varying from +++ to ++++ which were found to be negative on 3rd and 7th day post-treatment. The quantitative estimation of ketone bodies (acetone+acetoacetate) that revealed 15.56±0.202 mg/dl, 10.95±0.310 mg/dl and 14.42±0.325 mg/dl in urine, milk and blood were declined to 3.21±0.21 mg/dl, 2.77±0.09

mg/dl and 3.03±0.08 mg/dl in urine, milk and blood, respectively, in group III on 3rd day post-treatment which got further reduced to 1.76±0.21 mg/dl, 1.26±0.09 mg/dl and 1.52±0.08 mg/dl in urine, milk and blood on 7th day post-treatment by coming almost to normal range.

Biochemical profiles of serum insulin, plasma glucose, serum calcium and serum magnesium at different stages of treatment with allopathic drugs in group I, II and III are presented in Table 1. In the present investigation, the serum insulin level in ketotic cows at pre- and post-treatment showed similar trend following treatment having highest increase in group III (14.04±1.97 µ IU/l) (Table 1). Such big margin of difference between the values of serum insulin concentrations in ketotic and normal cows was observed because of the very grave impairment in carbohydrate metabolism and depression in secretion of insulin during ketonemia.

Blood glucose and insulin level were increased due to better efficacy of multi drug therapy with incorporation of glucocorticoid in the treatment of bovine ketosis (Nayak 1999, Panda 2003) who had adopted simultaneous administration of intravenous injection of glucose, oral administration of sodium propionate or propylene glycol and intramuscular administration of glucocorticoid for quicker and faster recovery from bovine ketosis. Following treatment, the plasma glucose levels in ketotic cows at pre- and post-treatment revealed similar trend having highest increase in group III (2.80±0.18 µ IU/l). The plasma glucose level was found to be significantly ($p < 0.05$) increased in ketotic cows as compared to group IV. This established a reverse correlation between glucose and ketone body levels in blood and direct correlation with insulin during ketosis (Klebaniuk *et al*. 2009). It was evident that decreased glucose level occurred during heavy lactational potential due to imbalance between demand and supply of glucose. During post calving lactational impairment of carbohydrate metabolism energy deficit occurred because of the increased demand for glucose by the mammary glands. The finding of low plasma glucose level during ketosis was in agreement with the findings of Nayak (1999) and Panda (2003) and Biswal (2006). The glucose requirements of the bovines are achieved by intermediary metabolism and lipid metabolism which play a key role in energy homeostasis. Similar findings were also recorded by Nayak (1999), Jena (2000) and Panda (2003) in the vicinity of Bhubaneswar city, Odisha.

The pre-treatment serum calcium was found to be 1.84±0.13 mmol /l which was increased to 2.27±0.24 mmol/L on 3rd day and 2.32±0.18 mmol/l ($p < 0.05$) on 7th day of post-treatment (Table 1). The low calcium level might be a transient biochemical phenomenon during ailment with ketosis due to lower input to meet the physiological demand of the dairy cows. In the same locality of Bhubaneswar, Nayak (1999) and Biswal (2006) recorded the serum calcium values to be depressed to 7.93 mg/dl, 8.35 mg/dl,1.85+0.017 mmol/l, 1.74±0.002 mmol/l, 1.73±0.002 mmol/l and 1.79±0.015 mmol/l, 1.49±0.41 mmol/l, respectively, in ketotic cows, which is in agreement with the present findings.

In the present investigation, the serum magnesium level in ketotic cows at pre- and post-treatment showed similar trend following treatment having highest increase in group I (0.98±0.009 mmol/l) (Table 1). The serum magnesium levels in ketotic cows were relatively higher in ketotic state as compared to the normal base line value of 0.95±0.008 mmol/l (Table 1). Johnson (1999) also reported similar level of serum magnesium in ketosis.

The biochemical profiles of plasma cholesterol, triglycerides and total protein in group I, II and III under allopathic treatment are shown in Table 1. The estimated plasma cholesterol levels were 4.39±0.07 mmol/l, 4.58±0.06 mmol/l and 4.70±0.09 mmol/l while 0.13±0.003 mmol/l, 0.15±0.004 mmol/l and 0.18±0.004 mmol/l for triglycerides, and 56.05±4.32 gm/l, 68.37±3.29 gm/l and 70.97±2.42 gm/l for total protein at pre-treatment, 3rd and 7th day post-treatment, respectively in Gr. III (Table 1). The increased value of plasma cholesterol and serum triglycerides in ketotic cows may be attributed to constant lipolysis and gluconeogenesis, increased mobilization to meet the energy deficit during ketosis (Panda 2003). During present investigation, the lower serum protein value may be due mainly to decreased supply of protein rich concentrate during anorectic stage of ketosis. During ketosis, the affected animals exhibited selective appetite for roughage and refused concentrate feeding. The quantum of ration was reduced substantially during ailment giving rise to low intake of protein. As the supply of protein from feed was decreased, it gave rise to decreased level of total protein during ketosis and the hepatic production of protein during ketosis might be inadequate (Kumar *et al.* 2001, Panda 2003, Farag and Metwally 2012).

Evaluation of the blood serum enzymes demonstrate the ability and functional biomarkers of liver and are possible in both physiological and pathological conditions leading to low production due to metabolic and nutritional disorders (Dezfouli *et al*. 2013). Following treatment in the present study, the ALT and AST levels observed in ketotic animals may be attributed to fatty liver changes which was decreased gradually following treatment in group III (27.42±1.88 unit /l) and (78.01±2.02 unit /l) on 7th day in group III (Farag and Metwally 2012). The serum ALP level was estimated as 89.07± 2.14 unit/l; 87.32± 2.43 unit/l, 86.24± 1.98 unit/l while the LDH level was 614.98±2.78 unit/l, 610.21 ±3.43 unit/l and 609.76 ±2.49

Table 2. Serum enzyme level showing improvement following treatment in ketotic dairy cows.

Group	ALT Unit/L			AST Unit/L			ALP Unit/L			LDH Unit/L		
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment		Pre-treatment	Post-treatment		Pre-treatment	Post treatment	
		3rd day	7thday		3rd day	7thday		3rd day	7thday		3rd day	7thday
I (n=10)	28.25 ±2.10	28.00 ±2.08	27.75 ±1.86	92.55 ±3.15	76.14 ±2.18	73.49 ±1.13*	89.60 ±2.22	87.98 ±2.26	86.84 ±3.22	614.23 ±3.47	610.61 ±3.43	610.12 ±3.46
II (n=10)	28.29 ±2.11	27.94 ±2.14	27.58 ±2.16	92.38 ±3.18	76.11 ±2.23	73.42 ±2.17*	89.57 ±2.23	87.89 ±3.24	86.44 ±2.16	614.44 ±2.80	610.33 ±2.78	609.87 ±2.76
III (n=10)	28.28 ±1.12	27.82 ±1.52	27.42 ±1.88	97.40 ±3.26	85.82 ±2.23	78.01 ±2.02*	89.07 ±2.14	87.32 ±2.43	86.24 ±1.98	614.98 ±2.78	610.21 ±3.43	609.76 ±2.49
IV (n=10)	28.24 ±2.10	28.30 ±1.99	28.34 ±2.09	92.53 ±2.16	92.66 ±3.76	92.81 ±2.14	89.58 ±2.84	89.63 ±3.22	89.69 ±3.22	614.20 ±3.85	614.48 ±3.37	614.54 ±3.67

*Superscripts within the columns differ statistically ($p < 0.05$).

unit/l at pre-treatment, 3rd and 7th day post-treatment, respectively (Table 2), in agreement with Sahinduran *et al*. (2010).

Concurring with the clinical improvement in treated animals, the biochemical and metabolic profiles in urine, milk and blood, serum insulin, plasma glucose, serum calcium, serum magnesium, plasma cholesterol, total protein, triglycerides, ALT, AST, ALP, and LDH approached to normal on 7th day post-treatment. Post-treatment ketotic indices showed that the effect of different allopathic drugs between the efficacy of drug packages, between the days within the drug packages and between days and between drug packages revealed highly significant difference ($p<0.05$) indicating the superiority of the drug package in group III over other therapeutic regimens.

Observation of milk yield

The group I animals under the treatment were accounted for the ketotic indices of 92.30±0.47 on 0 day at pre-treatment stage, 30.00±1.21 on 3rd day and 2.50±0.30 on 7th day post-treatment, respectively. The clinical improvement in these treated animals was observed to be 67.49% on 3rd day and 97.29% on 7th day post-treatment indicating that the drugs in group I were found to be efficacious for bovine ketosis.

In group II, there was clinical improvement on the respective days of post treatment and achieved to be 86.55% and 98.91% in these treated animals showing the efficacy of the drugs in an ascending manner. The mean ketotic index which was found to be 93.32±0.122% at pre-treatment stage in group II and III animals was declined to 7.70±1.19% on 3rd day and 0.00% on 7th day post-treatment. The clinical improvement was recorded as 91.74% on 3rd day and 100% on 7th day post-treatment indicating that the therapeutic regimen in this group was emerged to be fully efficacious in the treatment of bovine ketosis. The package of allopathic therapy in group II had an additional component of Decdan (dexamethasone) injection over the therapeutics for 3 days maintained blood glucose level in starvation during ketosis manifested 25.42% reduction of milk yield as compared to group I (25% reduction). The concomitant decrease in milk yield after treatment with glucocorticoid injection was also observed by Nayak (1999) and Panda (2003) in Bhubaneswar city with intravenous administration of Dextrose 25% and intramuscular injection of Hostacortin-H. The present findings of treatment with multi drug allopathic package were in agreement with the findings of the above workers.

The therapeutic regimen in group III was superior in efficacy as compared to other therapeutic packages under trial. Considering the aspects of shorter duration of treatment, faster amelioration of the clinical symptoms, quicker restoration of milk yield, quick retrieval of blood components to normalcy and speedy recovery rate, it could be concluded that the therapeutic package in group III was found to be the most efficacious in the treatment of bovine ketosis followed by the therapeutic packages in group I and II (Oetzel 2004). The therapeutic regimen for group III exhibited better performance than group II might be due to synergistic therapeutic effect of insulin which

stimulated the utilization of acetate by peripheral tissues and had the anabolic role in the control of glucose metabolism. Inclusion of insulin in therapeutic package was proved essential in the treatment of bovine ketosis with an aim of early recovery (Ismail *et al*. 2011). Brockman (1979) opined in the same line stating that the role of insulin was very much essential for the control of homeostasis of glucose in ketotic cows. Incorporation of Neohepatex injection in the treatment of bovine ketosis was considered as an ideal adjunct therapy in therapeutic regimen. Neohepatex injection, a liver stimulant and hepatoprotectant with hepatogenic and metabolic properties increased the gluconeogenic activity of the liver during ketosis, and overcome the risk factor of cobalt deficiency from anorexia, loss of condition and muscular weakness during ketosis.

CONCLUSION

The present study demonstrates that following standard treatment, the increased ALT and AST levels in ketotic animals attributed to fatty liver changes were decreased gradually in group III which was the most efficacious and superior therapeutic regimen practiced bringing the biochemical parameters to normal as compared to group I and II. An observation period of 14 days revealed the gradual increase of milk yield approaching to normalcy which was an evidence of no relapse of the disease after treatment.

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