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RESEARCH ARTICLE

COMPARATIVE EFFICACY OF CEFTRIAXONE, ENROFLOXACIN AND AMOXYCILLIN - CLOXACILLIN IN SUBCLINICAL MASTITIS AFFECTED COWS

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ABSTRACT

The study was conducted to evaluate the comparative efficacy of ceftriaxone, enrofloxacin and amoxycillin - cloxacillin for therapeutic management of subclinical mastitis affected cows. Ten apparently healthy Jersey crossbreed cows were taken as healthy control group. A total of 30 Jersey crossbred cows with history of reduction in milk yield were subjected to clinical examination, haematology and special examination of milk including bacterial culture and antibiotic sensitivity test. Based on antibiotic sensitivity test subclinical mastitis affected cows were divided into three treatment groups, each comprises 10 cows. The first group was treated with ceftriaxone, while the second and third groups were treated with enrofloxacin and amoxicillin - cloxacillin respectively. Whereas the healthy control group no treatment was advocated. Clinical examination of udder revealed no significant changes following therapy in all the three treatment groups. Haematological study of subclinical mastitis affected cows reveled leukocytosis with neutrophillia and eosinophillia before treatment and after treatment the haematological values reached the normal level. The physical examination of subclinical mastitic milk reveled no changes in colour, consistency and odour. The chemical examination reveled increased pH, electrical conductivity, somatic cell count, chloride content and positive scores of modified whiteside test and modified california mastitis test in subclinical mastitis affected cows before treatment and the values reached normal levels after treatment. The present study has shown better therapeutic efficacy of ceftriaxone compared to enrofloxacin and amoxycillin - cloxacillin in treatment of subclinical mastitis affected cows.

INTRODUCTION

Bovine mastitis is defined as inflammation of mammary gland with physical, chemical and bacteriological changes in milk and pathological changes in glandular tissue of the udder. It is multi-etiological complex, important, costly and highly prevalent disease of dairy animals which directly or indirectly affects the economy of the farmers and ultimately affects the economy of the country. It is major cause of economic loss to dairy industry globally. The global estimated economic losses per year due to mastitis amounts to 35 billion dollars (Sharma, 2007). Whereas in India the estimated monetary loss of over Rs. 6000 crore per year (Ranjan *et al.*, 2008). Most estimates show that on average an affected quarter suffers a 30% reduction in productivity and an affected cow loss of 15% of its production for the lactation (Duguma *et al.,* 2014). Bovine mastitis is mainly caused by bacteria and affects productivity in terms of both quality and quantity but also alter milk physical and chemical chracterstics (Silva *et al.,* 2012). Mastitis can be defined as clinical and subclinical (Zeryehun *et al*., 2013). Clinical mastitis is chracterised by physical, chemical and usually bacteriological changes in the milk such as presence of blood, water, pus containing clots, flakes and shreds consisting of fibrin and cellular debris and pathological changes in the glandular udder tissue (Fagiolo and Lai, 2007). Subclinical mastitis is chracterised by having no visible signs either in the udder or in the milk, but the milk production decreases and the somatic cell count increases (Kulkarni and Kaliwal, 2013). Therefore, it is not easily recognised by farmers and it can lead to large production losses (Hogeveen *et al.,* 2011). Higher incidence of subclinical mastitis in dairy herds and diversed etiology warrants, its proper management to reduce economic losses. Therefore, diagnosis and treatment of mastitis in subclinical stage itself is more important because it usually precedes the clinical form and become basis of herd problems when mastitis outbreaks occur. The therapy decisions in such cases are usually made empirically and antibiotic therapy is invariably considered. As antibiotic detection needs cultural sensitivity tests which are not available in Indian field conditions and indiscriminate use of antibiotics results in the emergence of resistant bacterial strains causing an increase in treatment failures (Varshney and Naresh, 2005). Hence, it has

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become inevitable for veterinarians to search for newer antibiotics and test their efficacy. Considering the above facts, the present study was conducted to study the comparative therapeutic efficacy of three antimicrobial drugs and cost of treatment in subclinical mastitis affected cows.

MATERIAL AND METHODS

Ten apparently healthy Jersey crossbred cows aged between 3 to 6 years stationed in and around Chennai city were selected and used as healthy control. The clinical study was conducted on 30 Jersey crossbred cows aged between 4 to 8 years brought to the Large Animal Clinic Medical Outpatient Unit, Department of Veterinary Clinical Medicine, Ethics and Jurisprudence, Madras Veterinary College, Chennai with the history of reduction in milk yield were confirmed as subclinical mastitis cases by chemical examination of milk including bacterial culture and subclinical mastitis cases were subjected to detailed routine Clinical examination (Boddie, 2000), Haematology (Coles, 1986) and Physical examination of milk (Saravanan, 1997), Chemical examination of milk: pH (Rosenberger, 1979), Electrical Conductivity (Hillerton and Walton, 1991), Chloride content (Yadav *et al*., 1993), Somatic Cell Count (Booth *et al.,* 1984), Modified White Side Test (Doxey, 1983) and Modified California Mastitis Test (Sharma and Rajani, 1969) during pre and post treatment. Based on clinical symptoms, laboratory and special examination of milk, the animals positive for subclinical mastitis were divided randomly based on *in vitro* antibiotic sensitivity test into three treatment groups each consisting 10 cows and efficacy of therapy was evaluated pre and post treatment. Animals in Group I were treated with ceftriaxone at a dose rate of 5 mg/kg body weight intramuscular once daily as well as 250 mg per quarter intramammary infusion once daily for 5 days. Animals in Group II were treated with enrofloxacin at a dose rate of 5 mg/kg body weight intramuscular once daily as well as 100 mg per quarter intramammary infusion once daily for 5 days. Animals in Group III were treated with amoxicillin - cloxacillin at a dose rate of 10 mg/kg body weight intramuscular twice daily as well as 250 mg per quarter intramammary infusion twice daily for 5 days. Apparently healthy control group was not given any treatment.

Statistical Analysis

The data obtained during the study were subjected to analysis of variance as per Snedecor and Cochran (1994).

RESULT AND DISCUSSION

In the present study, clinical examination of udder and milk revaled no significant change following therapy in all the three treatment groups in cows. It was on the expected line as there was no obvious change even before the treatment as the cases under this study were of subclinical mastitis. This observation is in agreement with Patnaik *et al.* (2013) who stated that no gross abnormality in milk and udder is noticed in subclinical mastitis. The colour, consistency and odour of milk samples collected from all subclinical mastitis affected cows were found normal and varied insignificantly during pre and post treatment, This observation is in agreement with Saravanan (1997) who stated that milk samples from all the positive cases of subclinical mastitis were found to have normal colour, consistency and odour. The mean haematological values of apparently healthy cows and cows with subclinical mastitis under different treatment trial are given in Tables 1. The pre treatment values of Hb, PCV and TEC of cows in group I, group II and group III did not differ significantly when compared to post treatment values of their respective control groups. There was no significant difference in the values of lymphocytes and monocytes between the pre and post treatment means. There was significant leukocytosis with neutrophilia and eosinophilia noticed in subclinical mastitis affected cows during pre treatment. The mean post treatment values of total leukocyte, neutrophil and eosinophil reduced significantly when compared to the pre treatment values of their respective groups and the values were comparable with that of the apparently healthy cows excepting the post treatment values of neutrophil in group III. Post treatment values showed significant decrease and were approaching towards their respective control values. It might be attributed to clinical efficacy of the treatment employed. With respect to group III (amoxycillin - cloxacillin), it could be noted that neutrophilic count in cows though decrease significantly from their pre treatment mean, remained still elevated above their respective control mean. Comparatively lower efficacy of the amoxycillin - cloxacillin (Table 4) might explain this change.

The values of various quantitative tests in apparently healthy cows and cows with subclinical mastitis are given in Tables 2. The mean milk pH values in cows with subclinical mastitis under group I (7.57 ± 0.05), group II (7.50 ± 0.00) and group III (7.56 ± 0.04) before treatment were found significantly ($P < 0.01$) elevated when compared to that of their control value (6.48 ± 0.01) (Table 2). The post treatment milk pH values of group I, II and III reduced significantly when compared to the respective mean pre treatment milk pH values of subclinical mastitis affected cows. The reduced post treatment milk pH values of group I was lesser than apparently healthy animals while that of group II were comparable to apparently healthy cows. Post treatment mean in group III showed a lowering trend towards apparently healthy cows (Table 2).

The mean pre treatment milk EC values of cows under group I, II and III were 6.83 ± 0.12 millisiemens / cm, 6.60 ± 0.10 millisiemens / cm and 6.72 ± 0.16 millisiemens / cm respectively and they were found to be significantly elevated when compared to that of control (4.78 ± 0.05 millisiemens / cm). Following treatment the mean milk EC in all the groups showed values comparable to the control group (Table 2). The mean pre treatment milk chloride content of cows under group I, II and III were 0.20 ± 0.00 g %, 0.20 ± 0.00 g % and 0.20 ± 0.00 g % respectively. It showed highly significantly difference ($P < 0.01$) when compared to that of their control value (0.11 ± 0.00 g %). The post treatment values of chloride of group I, II and III reduced significantly when compared to the pre treatment values and the same were comparable to the apparently healthy group (Table 2).

The mean pre treatment milk SCC of cows under group I, II and III were 297.23 ± 13.90 x 10^4 / ml, 274.42 ± 13.51 x 10^4 / ml and 271.55 ± 18.64 x 10^4 / ml respectively.

Table 1. Changes in haematological values after treatment of subclinical mastitis in cows

S. No.	Parameters	Apparently healthy control	Group I (Ceftriaxone)		Group II (Enrofloxacin)		Group III (Amoxycillin - Cloxacillin)		'F' value
			Pre treatment	Post treatment	Pre treatment	Post treatment	Pre treatment	Post treatment	
1.	Haemoglobin (g/dl)	8.98 ± 0.10	8.62 ± 0.20	8.44 ± 0.17	8.73 ± 0.19	8.33 ± 0.07	8.55 ± 0.18	8.62 ± 0.18	1.53
2.	Packed cell volume (per cent)	29.90 ± 0.34	29.40 ± 0.85	28.90 ± 0.76	29.60 ± 0.47	29.40 ± 0.42	29.20 ± 0.71	29.00 ± 0.63	0.30
3.	Total erythrocyte count (10^6 / cu. mm.)	5.29 ± 0.06	5.19 ± 0.11	5.27 ± 0.10	5.27 ± 0.10	5.18 ± 0.10	5.19 ± 0.10	5.15 ± 0.10	0.27
4.	Total leucocyte count (10^3 per cu. mm.)	7.80^a ± 1.13	8.89^b ± 1.47	7.64^a ± 1.08	8.98^b ± 1.38	7.92^a ± 1.32	8.87^b ± 4.20	7.91^a ± 4.28	5.56^{**}
5.	Neutrophils (10^3 per cu. mm.)	2.55^a ± 0.48	3.21^b ± 1.02	2.40^a ± 0.47	3.28^b ± 0.91	2.61^a ± 0.71	4.09^d ± 2.59	4.41^c ± 2.57	42.47^{**}
6.	Lymphocyte (10^3 per cu. mm.)	4.41 ± 0.33	4.50 ± 0.32	4.49 ± 0.32	4.54 ± 0.32	4.53 ± 0.31	4.51 ± 0.31	4.49 ± 0.34	1.15
7.	Monocyte (10^3 per cu. mm.)	0.24 ± 0.22	0.26 ± 0.26	0.22 ± 0.21	0.26 ± 0.34	0.24 ± 0.27	0.24 ± 0.25	0.21 ± 0.21	0.44
8.	Eosinophils (10^3 per cu. mm.)	0.26^a ± 0.19	0.45^b ± 0.55	0.22^a ± 0.19	0.45^b ± 0.49	0.27^a ± 0.25	0.42^b ± 0.35	0.28^a ± 0.26	7.65^{**}

Sample size in each group comprises of 10 cows.
Mean bearing the same superscript in the same column do not differ significantly.
**-Highly Significant

Table 2. Changes in pH, EC, Chloride content and SCC in milk after treatment of subclinical mastitis in cows

S. No.	Parameters	Apparently healthy control	Group I (Ceftriaxone)		Group II (Enrofloxacin)		Group III (Amoxycillin – Cloxacillin)		'F' value
			Pre treatment	Post treatment	Pre treatment	Post treatment	Pre treatment	Post treatment	
1.	pH	6.48^b ± 0.01	7.57^d ± 0.05	6.20^a ± 0.05	7.50^d ± 0.00	6.52^b ± 0.05	7.56^d ± 0.04	6.68^c ± 0.11	146.82^{**}
2.	Electrical Conductivity (millisiemens /cm)	4.78^b ± 0.05	6.83^c ± 0.12	4.27^a ± 0.06	6.60^c ± 0.10	4.83^b ± 0.12	6.72^c ± 0.16	5.05^b ± 0.22	83.99^{**}
3.	Chloride (gm%)	0.11^a ± 0.00	0.20^b ± 0.00	0.11^a ± 0.00	0.20^b ± 0.00	0.11^a ± 0.00	0.20^b ± 0.00	0.11^a ± 0.00	134.62^{**}
4.	Somatic Cell Count (SCC) (10^4 cells / ml)	4.38^a ± 0.11	297.23^b ± 13.90	4.31^a ± 0.12	274.42^b ± 13.51	9.95^a ± 4.54	271.55^b ± 18.64	18.18^a ± 6.30	259.36^{**}

Sample size in each group comprises of 10 cows.
Mean bearing the same superscript in the same column do not differ significantly.
**-Highly Significant

Table 3. Changes in MWST and MCMT scores after treatment of subclinical mastitis in cows

Treatment Groups	Scores	Cows			
		MWST		MCMT	
		Pre treatment	Post treatment	Pre treatment	Post treatment
Group I	+1	3 (15)	- (0)	2 (10)	- (0)
	+2	14 (70)	-(0)	15 (75)	- (0)
	+3	3 (15)	-(0)	3 (15)	- (0)
Group II	+1	6 (26.09)	6 (26.09)	4 (17.39)	4 (17.39)
	+2	15 (65.22)	-(0)	15 (65.22)	2 (6.25)
	+3	2 (8.69)	-(0)	4 (17.39)	- (0)
Group III	+1	4 (25)	4 (25)	2 (12.5)	2 (12.25)
	+2	11 (68.75)	-(0)	12 (75)	1 (6.25)
	+3	1 (6.25)	1 (6.25)	2 (12.5)	1 (6.25)

Figures in parenthesis indicate percentage.

Table 4. Comparative efficacy of antimicrobial drugs in subclinical mastitis of cows

Name of Drug	Cows		
	In vitro susceptibility (per cent)	Quarter cure rate (per cent)	Animal Cure rate (per cent)
Ceftriaxone (Group I)	89.83	100	100
Enrofloxacin (Group II)	88.13	86.95	80
Amoxycillin - Cloxacillin (Group III)	28.81 + 32.20	68.75	60

It showed highly significantly difference ($P < 0.01$) when compared to that of their control value ($4.38 \pm 0.11 \times 10^4$ / ml). The post treatment values of SCC of group I, II and III reduced significantly when compared to the pre treatment values and the same were comparable to the apparently healthy group (Table 2). In our study, the mean pre treatment milk pH, EC, chloride content and SCC values in cows affected with subclinical mastitis showed significant increase when compared to that of their respective control values (Table 2). After treatment, they decreased significantly when compared to their respective pre treatment values and were found approaching their respective control values in all the three treatment groups (Table 2). It could be attributed to sensitivity of pathogens towards ceftriaxone, enrofloxacin and amoxycillin - cloxacillin. In amoxycillin - cloxacillin treated group of cows, pH of milk though decrease significantly after treatment, still remained significantly elevated over that of control group. These changes could be very well related to comparatively lower efficacy of amoxycillin - cloxacillin in cows of this study. The MWST and MCMT score pre and post treatment values in cows with subclinical mastitis are given in Table 3. The reduction in the scores was more pronounced in group I followed by group II in cows following therapy. MWST and MCMT scores in subclinical mastitis varied from +1 to +3 in various treatment groups of cows (Table 3). After treatment with antibiotic in most of the cases, milk was restored to normalcy in cows. However, 2 cows in group II and 4 cows in group III were still reacting to MWST or MCMT with +1 or +2 score. These observations were indicative of slow return of biochemical changes in subclinical mastitis affected milk. The changes in leukogram also supported this interpretation.

Comparative efficacy of three different drugs against subclinical mastitis affected cows are presented in Table 4. Cows affected with subclinical mastitis and treated with ceftriaxone showed 100 per cent animal cure rate and 100 per cent quarter cure rate. Most of clinical cases recovered on the third day of treatment. The present observations also concurred with the report of Ramprabhu *et al.* (2004). In the present study, more number of cows in group I were affected with *Streptococci sp.* (60 per cent) and *E coli* (10 per cent). Ceftriaxone is the drug of choice for treating *Streptococcal* mastitis (Umakantan, 1998 and Ramprabhu *et al.,* 2004). Ceftriaxone is a bactericidal drug, belonging to third generation cephalosporin, which act by inhibiting bacterial cell wall synthesis. It had excellent efficacy against *Streptococcus sp.*, good against *Staphylococcus sp.* and remarkable activity against Enterobacteriaceae (Prescott and Baggot, 1994). Cows affected with subclinical mastitis and treated with enrofloxacin showed 80 per cent animal cure rate and 86.95 per cent quarter cure rate (Table 4) and most of the clinical cases recovered on fourth day of treatment. The present observations is in accordance with Akthar *et al.* (2004) who reported 84.62 per cent quarter cure rate in a clinical trial with enrofloxacin. Enrofloxacin is a bactericidal drug which belongs to fluroquinolones. Fluroquinolones are potent DNA gyrase inhibitor causing bactericidal action (Prescott and Baggot, 1994). In the present study, the efficacy of enrofloxacin was noticed to be lower than ceftriaxone; it might be due to development of resistance by bacterial strains because of its widespread, indiscriminate use in the treatment of mastitis in recent past. This observation is in agreement with Saranya *et al.* (2013) who stated that enrofloxacin and other fluoroquinolones are commonly used for treatment of mastitis and indiscriminate and unwarranted usages are the contributing factors for development of high level of resistance. Cows affected with subclinical mastitis and treated with amoxycillin – cloxacillin showed 60 per cent animal cure rate and 68.75 per cent quarter cure rate. In this group, only a few of the clinical cases recovered on the fifth day of treatment. It is in agreement with Tiwari and Sisodia (2000) who reported 50 per cent animal cure rate and 61.53 per cent quarter cure rate in a clinical trial with amoxycillin - cloxacillin through intramuscular and intracisternal routes. The lower efficacy of amoxycillin - cloxacillin noticed in the current study might be due to development of resistance from pathogenic bacteria towards commonly available antibiotics because of their widespread and indiscriminate use (Bhalerao *et al.,* 2000).

Comparison of *in vitro* sensitivity with *in vivo* efficacy of drug- A cursory view of the table 4. indicated that *in vivo* sensitivity of the drugs apparently correlated with *in vivo* efficacy. It is logical to expect 100 per cent treatment efficacy in all the groups as the antibiotic chosen was based on *in vitro* sensitivity. This observation is in agreement with Usha Rani *et al.* (2004) who stated that in some cases, the correlation between antimicrobial activity *in vitro* and *in vivo* was limited, a fact that turned to treatment failure and Pyorala (2009) who stated that antimicrobial susceptibility determined *in vitro* has been considered as a prerequisite for treatment and activity *in vitro* does not guarantee efficacy *in vivo* when treating bovine mastitis. Generally in clinical forms, organisms are considered either sensitive or resistant to the action of an antimicrobial. However, with many organism-antimicrobial associations, resistance or susceptibility is not an all or none phenomenon but is dependent upon drug concentration. Organisms which may be resistance to low level of an antimicrobial agent are frequently susceptible to its action at higher concentration (Blood and Radositis, 1989). The cost of treatment per animal in treatment trial with ceftriaxone, enrofloxacin and amoxycillin - cloxacillin were Rs. 86.18, Rs. 40.94 and Rs.

114.24 per animal per day respectively. It was found that the cost of treatment per animal was highest in amoxycillin - cloxacillin treatment group followed by ceftriaxone and enrofloxacin group. Ceftriaxone was found moderately costlier. However, by comparing the cost of treatment, the number of treatment required per day and the efficacy of ceftriaxone with that of other traditional antibiotics along with milk losses, cost of veterinary services and loss of quarter following clinical drug failure, it might be concluded that ceftriaxone was superior over other two antibiotics for the treatment of subclinical mastitis. It is in agreement with the report of Ramprabhu *et al*. (2004).

Conclusion

Subclinical mastitis is the dormant form of mastitis affecting dairy animals and responsible for the greatest economic losses associated with mastitis in dairy herds in the major dairy producing countries like India. The present study concluded that the only clinical sign observed in subclinical mastitis affected animals were reduction in milk yield. Leukogram and subclinical mastitic milk profile such as pH, electrical conductivity, chloride content, somatic cell count, MWST and MCMT scores can be used as indicator of clinical recovery of animals affected with subclinical mastitis. In our study, Ceftriaxone through intramuscular and intramammary routes were found to be highly effective and superior in comparison to enrofloxacin and amoxycillin - cloxacillin in treatment of subclinical mastitis affected cows.

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