



Novel Acaricides by Nanotechnology against Cattle Ticks and Their Effect on Physiological and Productive Performance

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A FIELD trial was conducted to evaluate the efficacy of capsules suspension formulation (CS) by nanotechnology and conventional acaricides against the cattle ticks (*Hyalomma marginatum*) and its effects on the body weight and blood parameters of Aberdeen angus cattle. Acaricides residues were determined in an animal's blood and milk. Thirty infested cattle were randomly divided into five groups, each one contains (3 bulls and 3 cows) based on the mean tick count. Results showed that, permethrin 25 % CS and lambda-cyhalothrin 10 % CS were significantly the most effective against ticks (2.7 and 3.8 ticks/animal, respectively) compared to fipronil 20 % SC and Acetamiprid 20 % SL (8.3 and 6.3 ticks/animal, respectively) after 70 days of treatment. Permethrin 25 % CS achieved 100 % control against highly ticks' infestation after 3 days of treatment and maintained for 56 days without its residues in blood and milk samples. Conversely, fipronil residue was detected in the cow's blood and milk (1.3 and 2.7 µg/l, respectively) however, it's non detected in bull's blood after 1 week of treatment. They gradually decreased to below detection limits after 3 and 6 weeks respectively. The animal body weight was significantly increased, additionally, the liver and kidney function were decreased to normal level in all treated animals. Finally, permethrin and lambda-cyhalothrin that formulated CS can be used as efficient acaricides and a safe alternative in tick control strategy in tropical areas.

Keywords: Cattle ticks, Acaricides, Nanotechnology, Pesticides, Weight gain, Biochemical analysis, Pesticides residues

Introduction

Ticks are the most important disease vector, which attack more than 80% of the world's cattle (FAO, 1984). Tick prevalence is viewed as a central point restricting the increasing livestock production worldwide and especially in tropical countries like Egypt (Kabir et al., 2011). Whereas, one tick specimen could transmit more infective pathogens cause many diseases such as theileriosis, babesiosis, anaplasmosis and cowdriosis (Piesman et al., 1986; Fuente et al., 2008; Liyanaarachchi et al., 2013). These diseases diminish cow's growth rate, fertility,

milk production and quality hides which results in significant economic losses to livestock breeders. (Pegram and Oosterwijk, 1990; Jongejan and Uilenberg, 1994).

The chemical control remains the main choice for tick control that based on the regular and frequent used of synthetic pesticides in most countries. (De Castro, 1997; Lopes et al., 2013). Inappropriate and frequent use of these pesticides often leads to resistance development in tick, which has made control difficult in some breeding areas. (Kunz and Kemp, 1994; Hassanain et al., 1997; George et al., 2004; Li et al., 2004; Rosado-

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Aguilar *et al.*, 2008). Moreover, adjacent to their potential toxic effects on the animals and nontarget organisms, these chemicals can produce residues in animal products and have serious impacts on the consumer's health and environment (Laffont *et al.*, 2001; Graf *et al.*, 2004). So, worldwide researchers are making a great effort to develop the most efficient methods for tick control. However, chemical control with acaricides was considered as one of the best methods (Rajput *et al.*, 2006), but conventional pesticides are firmly connected with environmental degradation and health hazards. This is due to pesticide toxicity, non-biodegradability and the inexactitude of some formulations. This amalgamation of side effects and low efficiency is the motivation for a rethinking of conventional pesticide use.

Nanotechnology provides promising responses to these multiple challenges and have ecological earnings (Liu *et al.*, 2008 and Froggett, 2009). Due to the higher efficacy of nano-active ingredients, it allows for the reduction of pesticide volumes, hence minimize many previous pesticide problems and lower costs (Barik *et al.*, 2008; Stadler *et al.*, 2010 and Goswami *et al.*, 2010). Therefore, the aim of this study to evaluate the efficacy of nanocapsule-formation of acaricides that help continues tick 's control. In addition to, prevent production loss, reduce pesticide residues in cattle products and their impacts on animal physiology.

Materials and methods

Study site and animals

The present study was conducted at the experimental Farm of Animal Production Department, Faculty of Agriculture, New Valley University, El-kharga City (25°31'26" N, 30°36'33" E, altitude 283 m) located about 10 km off the New Valley government road to Assiut. The climate of this area is arid and dry, essentially that of the desert. A seventy days study was carried out on Aberdeen Angus cows heifer and Bull. Cows and bulls averaged 317.20-381.30 kg and 337.26- 395.67 kg body weight (BW). The age was average 1.5-3 years. The animals were fed in groups to concentrate fed mixture, hay and wheat straw according to NRC (2000) requirements. The experiment was carried out following the procedures approved by the Ethics Committee on Animal Experimentation of New Valley University, Faculty of Veterinary.

Acaricides used

Four commercial pesticides were tested against cow's tick infestation as active ingredient recommended by WHO (1997). Acetamiprid (Beticol® 20% SL, Maytrade, Giza, Egypt), fipronil (Coach® 20 % SC, Shoura Chemical, Cairo, Egypt), Permethrin (Permixon® 25% CS, Deeval Ltd, Flintshire, UK) and α -Cyhalothrin (Tornado® 10% CS, Deeval Ltd). They had been sprayed at the rates (0.7, 0.35, 0.25 and 0.1 gm/L/ animal respectively). Tornado® 10% CS and Permixon® 25% CS acaricides were a nano-capsule suspension (CS) and controlled release formulation (CRF) by nanotechnology.

Experimental design and procedure

Thirty Aberdeen Angus cattles infected with ticks normally, kept on the farm, were used in a completely randomized design experiment. All animals were divided randomly into five equal groups (3 cows and 3 bulls each group) based on pre-treatment live tick count. Four acaricides treatments groups and water alone for an untreated group (negative control). The experiment was conducted from October to December 2017 for 10 weeks. Prior to the commencement of the study, the strategic policy for tick management of the production animal farm was a spot treatment for animals using a portable electric ULV sprayer (Model SF-YM05A) once a time. Cattle's surrounding environment (bedding material, wall, fomites, etc..) was sprayed three times in 14-day intervals using a backpack sprayer. During spraying or sampling, each animal was held in the neck region using a cattle crush to restrain it. Animals in different treatment groups were kept in separate paddocks which had been administered in the same way during the study period.

Monitoring and evaluation

Ticks number

The Cattle were inspected quantitatively through "finger counting" (Rugg and Hair, 2007) of the ticks on one side of the body and double the number to get the entire body count (Knopf *et al.* 2002, Walker *et al.*, 2003). The efficacy of different treatments (%) was calculated at 0, 1, 3, 7, 14, 28, 42, 56 and 70 days. The percentage of efficacy against cow's ticks, *Hyalomma marginatum* was calculated using arithmetic means, according to the formula proposed by Roulston *et al.* (1968), described below:

$$\text{Percentage of efficacy} = \left(1 - \frac{T_a}{T_b} \times \frac{C_b}{C_a}\right) \times 100$$

where T_a is the mean number of ticks counted on treated animals after treatment; T_b the mean

number of ticks counted on treated animals one day before treatment; C_a the mean number of ticks counted on control animals after the experiment started; C_b the mean number of ticks counted on control animals one day before treatment.

Productive performance

The body weight (BW) of all groups was recorded at the beginning of the experimental period (initial weight) and after 14, 28, 42, 56 and 70 days in order to detect any changes that may take place. Cattles were weighed in the morning (07:00 h, before feeding) to obtain the body weight (bw). The percentage body weight gain was calculated according to the equation below; -

$$\% \text{ body weight gain} = \frac{(\text{final b.w.} - \text{initial b.w.})}{(\text{initial b.w.})} \times 100$$

Sampling of blood serum and milk

Blood samples via jugular venipuncture were collected from each animal before the morning feeding during period 0, 1, 3 and 6 weeks of starting the experiment. Blood samples were decanted into sterile test tubes without anticoagulant for obtaining serum. The collected blood samples were quickly kept in ice pack and sent to the laboratory. Serum samples were obtained by centrifugation of blood samples in the second tube for 10 minutes at 3,000 r.p.m, then dispensed into two 2 ml Eppendorf tubes and stored at -20 °C for blood parameter analysis and pesticide residues. Milk samples were taken at 0, 1, 3, and 6 weeks throughout the suckling period from all cows in different treatments. The samples were taken in the morning and afternoon and then both samples were mixed together then dispensed into 50 ml Eppendorf tube and stored at -20 °C for determine acaricides residues. The sample that collected by hand milking of both sides of the udder and pooled into one sample per cow.

Pesticides residue analysis

Chemicals

Acetonitrile (HPLC, assay > 99%), methanol 99.9% HPLC grade, formic acid 98-100% and ammonia solution 33% were purchased from Sigma-Aldrich, USA. De-ionized water was produced by a mille poreunit (Mille-Q®, Integral Water Purification System, USA). The Agilent QuEChERS extraction kit was used for extraction it consisted of Buffer 1 (4 g magnesium sulphate; 1 g sodium chloride; 1 g trisodium citrate dihydrate and 0.5 g disodium hydrogencitrate sesquihydrate).

Extraction and procedure

Quick Easy Cheap Effective Rugged Safe (QuEChERS) pesticides extraction was performed following the description of Anastassiades et al. (2003). Five ml milk and 1 ml blood serum (W) sample were weighed in 50 ml PFTE tube, 1 ml acetonitrile was added for blood serum samples and 5 ml for milk samples then shaken for one minute. The buffer 1 was added and the sample was shaken immediately for one minute. The sample was centrifuged at 4000 rpm for 5 minutes. The sample was filtrated using syringe filter and directly injected into LC-MS/MS system.

Analytical conditions

Acaricides residues were analyzed by LC-MS/MS system, LC-MS/MS was performed with an Agilent 1200 Series HPLC instrument coupled to an API 4000 Qtrap MS/MS from Applied Biosystems with electrospray ionisation (ESI) interface. Separation was performed on a C18 column ZORBAX Eclipse XDB-C18 4.6 x 150 mm, 5 µm particle size. The injection volume was 25 µl. A gradient elution program at 0.3 mL/min flow, in which one reservoir contained 10 mM ammonium formate solution in methanol-water (1:9) and the other contained methanol was used. The ESI source was used in the positive mode, and N2 nebulizer, curtain, and other gas settings were optimized according to recommendations made by the manufacturer; the source temperature was 300°C, ion spray potential, 5500 V. The Multiple Reaction Monitoring mode (MRM) was used for determination of examined pesticides. The test method showed that limit of detection was 1 µg/l while the limit of quantification was 3 µg/l. The average recovery for test method varied between 70 % and 120 %.

Biochemical analysis

Serum samples were analyzed for alanine aminotransferase (ALT), aspartate aminotransferase (AST) as described by Reitman and Frankel (1957), blood serum urea-N (Henry, 1966) and creatinine (Cr) by Bartels and Bohmer (1971) were determined using appropriate commercial test kits (Spectrum Company, Egypt). The concentrations were measured using standard protocols (Photometer 5010 v5+, Riele Co., Berlin, Germany).

Statistical analysis

The reduction and body weight gain percentages were subjected to transformation as described by Wadley (1967) where each value (x) was transformed to $\frac{x}{\sqrt{x+0.5}}$ and then these

transformed values were statistically analyzed because there were values of 0.00%. Analysis of variance (ANOVA) was carried out using Proc Mixed of SAS package version 9.2 (SAS 2008) and means were compared by Duncan comparison at 5 % level of significance (Steel and Torrie, 1981).

Results

Efficacy of acaricides

Tick infestation

The results of the statistical analysis regarding the main effect of acaricides on the tick count at intervals different times are shown in Fig. 1. Lambda-cyhalothrin 10 % CS and fipronil 20 % SC achieved the highest reduction of ticks after 24 hr of treatment. On the other hand, acetamiprid 20% SL was the lowest efficacy on ticks. Permethrin 25 % CS was the fastest acaricide and achieved 100 % of tick's reduction after 3 days of treatment, while the rest of acaricides peaked at 100 % at day 7th post-treatment. In addition, the recurrence of the tick infestation was started again on treated cattle with permethrin and fipronil acaricides (2.17 and 8 ticks/animal respectively) at day 14th post-treatments. While, the infestation was increased with all acaricides acetamiprid, Fipronil, lambda-cyhalothrin and permethrin (1.17, 8, 2.17 and 6.83 ticks/animal) respectively at day 28th post-treatment. Over time, the ticks, numbers disappeared again where the reduction rate peaked at 100% at day 42th after treatment. This

result continued until 56 days without treatment repeated except efficacy of fipronil. However, permethrin has the longest effectiveness period with the lowest mean number of ticks 2.7/animal while, the highest mean number of ticks was 8.2 and 6.3 ticks/animal for fipronil and acetamiprid respectively at day 70th post-treatment.

Influence of sex type of cattle on tick infestation showed that, there was more significant increasing in the infestation of ticks on cows at a value of 114.8 ticks/animal than bulls 106.8 ticks/animal before treatments at zero time (Table 1). However, over time and a significant decrease in tick numbers for treated animals, bulls were significantly more likely to be infected than cows at 70 days post treatment. The differences in reduction percentages of tick counts between the two sexes of cattle treated with acaricides are shown in Table 1. The highest decreases of tick infestation after 24 hr of treatment was 98.2 % and 97.5 % on treated cows with fipronil and lambda-cyhalothrin acaricides respectively, without any significant difference between them, while the acetamiprid gave the lowest percentage on cows and bulls with a significant difference 87.3 % and 81.4 % respectively. All acaricides reduced the tick infestation at 100 % after 3 days of treatments on cows only, while the lowest percentages were 98 %, 97 %, 97.8 % for acetamiprid, fipronil and lambda-cyhalothrin acaricides respectively on bulls which reached to 100 % at day 7th post-treatment.

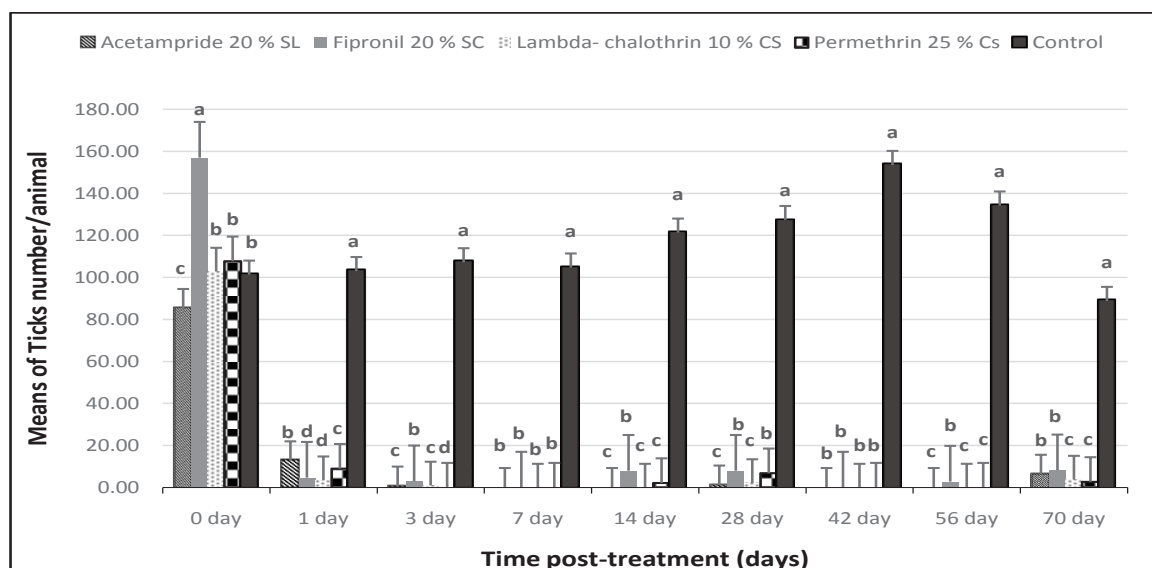


Fig. 1. The mean of tick count following a single treatment with a novel acaricides at different times post-treatment. Values followed by the same letters within the same period are not significantly different at 5% according to Duncan's multiple range test. SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension (CS) by nanotechnology.

TABLE 1. Efficacy of novel acaricides against cattle ticks, *Hyalomma marginatum* at interval times of field treatment.

Acaricides	Cattle Sex	Means						
		Day 0	Day 1		Day 3		Day 7	
			No	E%	No	E %	No	E%
Acetamiprid 20 % SL	M	60.0 ^g	11.3 ^{cd}	81.4 ^e	1.3 ^d	98.0 ^b	00.0 ^c	100 ^a
	F	110.3 ^d	14.0 ^c	87.3 ^d	0.0 ^d	100 ^a	00.0 ^c	100 ^a
Fipronil 20 % SC	M	185.7 ^a	07.0 ^{ef}	96.3 ^{ab}	6.0 ^c	97.0 ^c	00.0 ^c	100 ^a
	F	128.3 ^b	02.3 ^g	98.2 ^a	0.0 ^d	100 ^a	00.0 ^c	100 ^a
Lambda-cyhalothrin 10 % CS	M	86.0 ^f	04.0 ^{fg}	95.4 ^b	2.0 ^d	97.8 ^b	00.0 ^c	100 ^a
	F	119.7 ^c	03.0 ^g	97.5 ^{ab}	0.0 ^d	100 ^a	00.0 ^c	100 ^a
Permethrin 25 % CS	M	114.0 ^{cd}	08.3 ^{de}	92.8 ^c	0.0 ^d	100 ^a	00.0 ^c	100 ^a
	F	101.3 ^d	09.7 ^{de}	90.6 ^c	0.0 ^d	100 ^a	00.0 ^c	100 ^a
Untreated Control 0 %	M	88.3 ^f	90.0 ^b	00.0 ^f	94.0 ^b	00.0 ^d	91.0 ^b	00.0 ^b
	F	114.3 ^{cd}	116.0 ^a	00.0 ^f	120.3 ^a	00.0 ^d	118.3 ^a	00.0 ^b
Means	M	106.8 ^b	24.0 ^b	73.2 ^b	20.7 ^b	78.5 ^b	18.2 ^b	80.0 ^a
	F	114.8 ^a	29.0 ^a	74.7 ^a	24.1 ^a	80.0 ^a	23.7 ^a	80.0 ^a

M: Male (bull); F: Female (cow); E%: Efficacy percentage; No: number of ticks per animal; SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension by nanotechnology.

Values followed by the same letters within a column are not significantly differed at 5% according to Duncan's multiple range test.

The tick re-infestation data in (Table 2) showed that, the tick infestation appeared again on treated bulls by fipronil with an average of 16 ticks/animal, where the efficacy percentage decreased to 92.8% at day 14th post-treatment. In contrast the infection appeared first on treated cows by permethrin, which decreased its efficacy percent to 96.4 %. Tick counts were increased until day 28th post-treatment without any significant differences between bulls and cows for all treatments, except treated cattle with fipronil (13 ticks/bull and 3 ticks/cow). All acaricides treatments achieved 100% efficacy again at day 42th post-treatment and continued for 56 days after treatment except treated bulls with fipronil achieved 97.8% (5.7 ticks/animal) without repeated of acaricides treatments. However, at day 70th post-treatment the efficacy of all acaricides on treated bulls was significantly reduced compared to cows. In addition, permethrin treatment accomplished the longest effectiveness period on bulls and cows with the lowest mean number of ticks 4.3 and 1.0

ticks /animal respectively, compared to control group and other acaricides.

Bovines performance

At the beginning of the study (before treatment, day 0), all infected cattle may be losing their weight as a result of tick infestation in all groups without any significant difference between them. However, the body weight loss of treated animals was significantly higher ($P < 0.05$) than control at 14th day post-treatment (Fig. 2). It was continued of loss increasing until day 28th post-treatments then, started to decrease at day 42th post-treatments. The body weight gain appeared at day 56 and 70 post-treatment in both bulls and cows. Finally, the present study indicated the permethrin 25% CS and fipronil 20 % SC treatments had highly beneficial impact on weight gain percentages (7.78 and 7.92 %) respectively. There was no significant difference in body weight gain between treated cattle with all acaricides at end of experimented.

TABLE 2. Efficacy of novel acaricides against cattle ticks, *Hyalomma marginatum* at re-infestation periods.

Acaricides	Cattle Sex	Means										
		Day 0	Day 14		Day 28		Day 42		Day 56		Day 70	
			No	E %	No	E %	No	E %	No	E %	No	E %
Acetamiprid 20 % SL	M	60.0 ^e	00.0 ^e	100 ^a	1.7 ^e	97.8 ^a	00.0 ^e	100 ^a	00.0 ^d	100 ^a	09.0 ^e	84.5 ^e
	F	110.3 ^d	00.0 ^e	100 ^a	0.7 ^e	99.5 ^a	00.0 ^e	100 ^a	00.0 ^d	100 ^a	03.7 ^{bc}	95.8 ^{bc}
Fipronil 20 % SC	M	185.7 ^a	16.0 ^e	92.8 ^c	13 ^c	94.5 ^b	00.0 ^e	100 ^a	05.7 ^c	97.8 ^b	11.7 ^c	93.5 ^d
	F	128.3 ^b	00.0 ^e	100 ^a	3.0 ^e	98.1 ^a	00.0 ^e	100 ^a	00.0 ^d	100 ^a	04.7 ^d	95.5 ^c
Lambda-cyhalothrin 10 % CS	M	86.0 ^f	00.0 ^e	100 ^a	2.0 ^e	98.1 ^a	00.0 ^e	100 ^a	00.0 ^d	100 ^a	05.3 ^d	93.6 ^d
	F	119.7 ^c	00.0 ^e	100 ^a	2.3 ^e	98.4 ^a	00.0 ^e	100 ^a	00.0 ^d	100 ^a	02.3 ^{bc}	97.5 ^{ab}
Permethrin 25 % CS	M	114.0 ^{cd}	00.0 ^e	100 ^a	6.3 ^d	95.6 ^b	00.0 ^e	100 ^a	00.0 ^d	100 ^a	04.3 ^{bc}	96.0 ^{bc}
	F	101.3 ^d	04.3 ^d	96.4 ^b	7.3 ^d	94.2 ^b	00.0 ^e	100 ^a	00.0 ^d	100 ^a	01.0 ^e	98.8 ^a
Untreated Control 0 %	M	88.3 ^f	105.7 ^b	00.0 ^d	112.0 ^b	00.0 ^e	139 ^b	00.0 ^b	122.3 ^b	00.0 ^e	85.7 ^b	00.0 ^f
	F	114.3 ^{cd}	137.0 ^a	00.0 ^d	142.7 ^a	00.0 ^e	168 ^a	00.0 ^b	146.0 ^a	00.0 ^e	92.0 ^a	00.0 ^f
Means	M	106.8 ^b	24.3 ^b	78.6 ^a	27.0 ^b	77.2 ^b	27.8 ^b	80.0 ^a	25.6 ^b	79.6 ^b	23.2 ^a	73.5 ^b
	F	114.8 ^a	28.3 ^a	79.2 ^a	31.2 ^a	78.0 ^a	33.6 ^a	80.0 ^a	29.2 ^a	80.0 ^a	20.7 ^b	77.5 ^a

M: Male (bull); F: Female (cow); E%: Efficacy percentage; No: number of ticks per animal; SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension (CS) by nanotechnology.

Values followed by the same letters within a column are not significantly differed at 5% according to Duncan's multiple range test.

Liver and kidney functions

Liver enzyme concentrations, blood serum alanine aminotransferase (ALT, U/l) and aspartate aminotransferase (AST, U/l) at week 0, after 1, 3 and 6 weeks of the experimental periods in male and female Aberdeen Angus cattle are presented in Tables 3 and 4. The differences in AST and ALT mean values (regardless of sex) were not significant at the beginning of the study, while the values were differed significantly ($P < 0.05$) at 1, 3 and 6 weeks than untreated animals. The results also indicated that the mean values of AST and ALT concentrations (regardless of sex) significantly ($P < 0.05$) decreased gradually with the advancement of the experimental periods in all treated animals. Permethrin 25 % CS has a significantly lower value of the ALT (21.0 ± 1.75) and AST (61.0 ± 1.87) U/l than the control group (30.0 ± 1.16) and (80.8 ± 3.94) U/l, respectively. There wasn't any significant effect of sex on all acaricides treatments beginning of 3rd week post-treatment.

Blood serum Urea-N (BUN) and creatinine (Cr) concentrations at week 0, after 1, 3 and 6 weeks of the experimental periods in males and females of Aberdeen Angus cattle are presented in Tables 5 and 6. There was no significant difference of Urea-N (BUN) and Creatinine (Cr) concentrations at week 0 (pre-treatment) between all animals. BUN and Cr concentrations were significantly decreased ($P < 0.05$) in treated groups if compared to the untreated group at 1, 3 and 6-weeks post treatment. Permethrin 25 % CS had significant low value for the creatinine (1.5 ± 0.05 mg/dl) but Permethrin 25 % CS and fipronil 20% SC had significant low value for BUN (19.9 ± 0.90 and 19.8 ± 0.62 mg/dl respectively) compared the control group. Concerning the main effect of sex on BUN and Cr values, it can be observed that there were no significant differences between males and females in pre-treatments and continues to the end of experimental for BUN conversely, Cr has significant differences between two sexes at post-treatment periods.

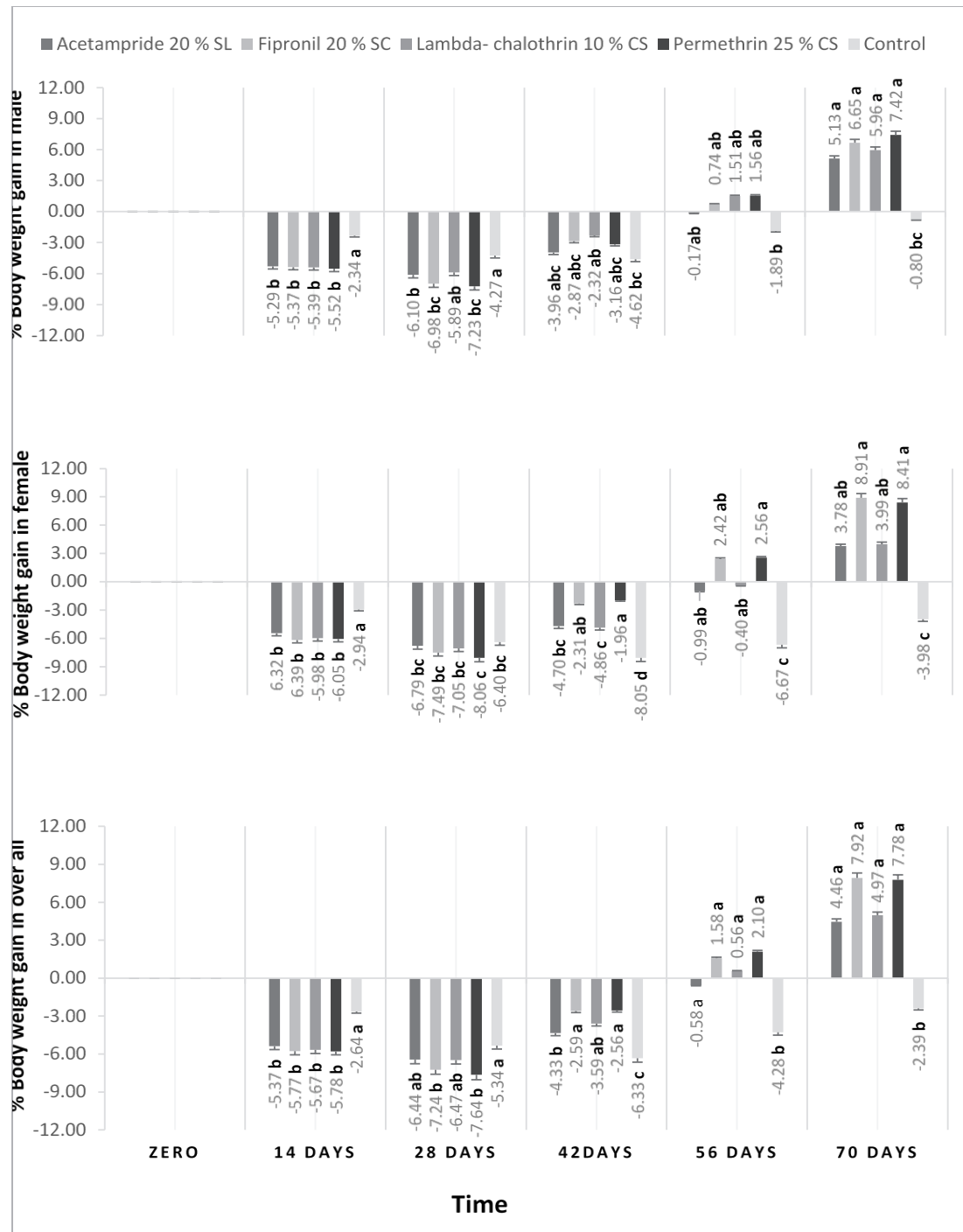


Fig. 2. The mean of body weight gain of two sex following a single treatment with a novel acaricides at different times post-treatment. Values followed by the same letters within a same period are not significantly differed at 5% according to Duncan's multiple range test. SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension (CS) by nanotechnology.

TABLE 3. Efficacy of novel acaricides and tick's infestation on liver enzymes, alanine aminotransferase (ALT) in blood serum of two cattlesexes.

Acaricides	Cattle Sex	Mean \pm SD							
		Week 0	Means	Week1	Means	Week3	Means	Week 6	Means
Acetamiprid 20 % SL	M	34.3 \pm 1.88 ^b	35.5 \pm 4.25 ^a	30.2 \pm 1.29 ^{cd}	30.4 \pm 0.88 ^b	26.0 \pm 1.90 ^b	26.2 \pm 2.00 ^b	22.9 \pm 1.58 ^b	22.5 \pm 1.87 ^b
	F	36.6 \pm 6.15 ^{ab}		30.6 \pm 0.42 ^c		26.4 \pm 2.54 ^b		22.1 \pm 2.40 ^{bc}	
Fipronil 20 % SC	M	37.4 \pm 0.44 ^{ab}	36.1 \pm 2.16 ^a	30.4 \pm 1.58 ^{cd}	29.4 \pm 1.57 ^b	25.0 \pm 1.27 ^b	24.5 \pm 1.36 ^b	21.0 \pm 0.96 ^{bc}	20.7 \pm 0.92 ^c
	F	34.9 \pm 2.55 ^{ab}		28.5 \pm 0.86 ^{de}		24.0 \pm 1.53 ^b		20.4 \pm 0.99 ^c	
Lambda- cyhalothrin 10 % CS	M	36.9 \pm 0.58 ^{ab}	35.2 \pm 1.96 ^a	31.1 \pm 1.15 ^c	30.3 \pm 1.61 ^b	25.3 \pm 1.50 ^b	25.2 \pm 1.44 ^b	22.3 \pm 1.65 ^{bc}	21.2 \pm 1.67 ^{bc}
	F	33.6 \pm 1.00 ^b		29.5 \pm 1.80 ^{de}		25.1 \pm 1.72 ^b		20.2 \pm 1.01 ^c	
Permethrin 25 % CS	M	39.4 \pm 0.88 ^a	36.2 \pm 3.99 ^a	31.2 \pm 0.45 ^c	29.6 \pm 1.75 ^b	25.6 \pm 1.31 ^b	24.8 \pm 1.60 ^b	20.9 \pm 1.15 ^{bc}	21.0 \pm 1.75 ^{bc}
	F	33.0 \pm 2.92 ^b		28.1 \pm 0.52 ^e		23.9 \pm 1.64 ^b		21.1 \pm 2.49 ^{bc}	
Untreated Control 0 %	M	37.6 \pm 1.25 ^{ab}	35.6 \pm 2.61 ^a	36.7 \pm 0.90 ^a	35.5 \pm 1.52 ^a	33.5 \pm 1.03 ^a	32.5 \pm 1.26 ^a	30.1 \pm 1.70 ^a	30.0 \pm 1.16 ^a
	F	33.6 \pm 1.81 ^b		34.2 \pm 0.59 ^b		31.6 \pm 0.34 ^a		29.8 \pm 0.65 ^a	
Means	M	37.1 \pm 1.94 ^a	-----	32.0 \pm 2.68 ^a	-----	27.1 \pm 3.56 ^a	-----	22.7 \pm 4.00 ^a	-----
	F	34.3 \pm 3.15 ^b	-----	30.2 \pm 2.44 ^b	-----	26.2 \pm 3.26 ^a	-----	23.4 \pm 3.75 ^a	-----

M: Male (bull); F: Female (cow); SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension by nanotechnology
 Values followed by the same letters within a column are not significantly differed at 5% according to Duncan's multiple range test.

TABLE 4. Efficacy of novel acaricides and tick's infestation on liver enzymes, aspartate aminotransferase (AST) in blood serum of two cattle sexes.

Acaricides	Cattle Sex	Mean \pm SD							
		Week 0	Means	Week1	Means	Week3	Means	Week 6	Means
Acetamiprid 20 % SL	M	90.2 \pm 2.36 ^a	88.8 \pm 2.65 ^a	85.7 \pm 4.15 ^{bc}	84.2 \pm 3.63 ^b	74.6 \pm 1.06 ^c	73.3 \pm 2.10 ^b	62.0 \pm 2.17 ^b	63.7 \pm 2.36 ^b
	F	87.4 \pm 2.55 ^a		82.7 \pm 2.98 ^{cd}		71.9 \pm 2.14 ^{cd}		65.3 \pm 1.00 ^b	
Fipronil 20 % SC	M	89.5 \pm 3.47 ^a	88.6 \pm 3.40 ^a	85.2 \pm 3.64 ^{bcd}	83.3 \pm 3.61 ^b	71.4 \pm 1.03 ^d	71.5 \pm 1.48 ^b	62.0 \pm 2.94 ^b	62.1 \pm 3.07 ^b
	F	87.6 \pm 3.76 ^a		81.4 \pm 2.88 ^d		71.5 \pm 2.09 ^d		62.1 \pm 3.85 ^b	
Lambda-cyhalothrin 10 % CS	M	87.7 \pm 3.05 ^a	88.3 \pm 2.84 ^a	84.0 \pm 3.78 ^{cd}	84.8 \pm 2.85 ^b	71.1 \pm 1.55 ^d	72.1 \pm 2.05 ^b	61.4 \pm 4.02 ^b	62.5 \pm 3.54 ^b
	F	88.7 \pm 3.17 ^a		85.6 \pm 2.03 ^{bc}		73.1 \pm 2.24 ^{cd}		63.6 \pm 3.38 ^b	
Permethrin 25 % CS	M	87.8 \pm 3.37 ^a	88.00 \pm 3.6 ^a	83.7 \pm 2.53 ^{cd}	83.9 \pm 3.50 ^b	71.2 \pm 1.12 ^d	71.2 \pm 1.47 ^b	61.5 \pm 2.20 ^b	61.0 \pm 1.87 ^b
	F	88.2 \pm 4.71 ^a		84.1 \pm 4.91 ^{cd}		71.2 \pm 2.04 ^d		60.5 \pm 1.73 ^b	
Untreated Control 0 %	M	87.5 \pm 2.44 ^a	88.3 \pm 2.59 ^a	88.1 \pm 1.90 ^{ab}	89.3 \pm 1.97 ^a	85.9 \pm 2.52 ^b	87.4 \pm 2.70 ^a	81.0 \pm 4.22 ^a	80.8 \pm 3.94 ^a
	F	89.0 \pm 2.99 ^a		90.4 \pm 1.51 ^a		88.9 \pm 2.25 ^a		80.6 \pm 4.56 ^a	
Means	M	88.5 \pm 2.75 ^a	-----	85.4 \pm 3.24 ^a	-----	74.9 \pm 6.02 ^a	-----	65.6 \pm 8.45 ^a	-----
	F	88.2 \pm 3.04 ^a	-----	84.8 \pm 4.15 ^a	-----	75.3 \pm 7.30 ^a	-----	66.4 \pm 7.98 ^a	-----

M: Male (bull); F: Female (cow); SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension by nanotechnology
 Values followed by the same letters within a column are not significantly differed at 5% according to Duncan's multiple range test.

TABLE 5. Efficacy of novel acaricides and tick's infestation on kidney enzymes, urea-N (BUN) in blood serum of two cattle sexes.

Acaricides	Cattle Sex	Mean \pm SD							
		Week 0	Means	Week1	Means	Week3	Means	Week 6	Means
Acetamiprid	M	28.4 \pm 2.94 ^a		26.9 \pm 2.71 ^b		22.7 \pm 1.54 ^b		19.4 \pm 0.94 ^b	
20 % SL	F	28.4 \pm 0.68 ^a	28.4 \pm 1.91 ^a	25.6 \pm 1.14 ^b	26.3 \pm 1.98 ^b	21.5 \pm 0.75 ^b	22.1 \pm 1.26 ^b	20.6 \pm 0.58 ^b	20.0 \pm 0.99 ^b
Fipronil	M	27.9 \pm 1.05 ^a		24.3 \pm 0.62 ^b		21.3 \pm 0.99 ^b		20.0 \pm 0.33 ^b	
20 % SC	F	29.7 \pm 0.40 ^a	28.8 \pm 1.21 ^a	26.0 \pm 0.55 ^b	25.1 \pm 1.08 ^b	22.3 \pm 0.88 ^b	21.8 \pm 0.98 ^b	19.5 \pm 0.84 ^b	19.8 \pm 0.62 ^b
Lambda-cyhalothrin	M	29.1 \pm 0.99 ^a		26.1 \pm 1.68 ^b		22.9 \pm 3.00 ^b		21.2 \pm 0.44 ^b	
10 % CS	F	29.3 \pm 0.60 ^a	29.2 \pm 0.74 ^a	26.53 \pm 1.28 ^b	26.3 \pm 1.35 ^b	22.0 \pm 0.56 ^b	22.5 \pm 2.00 ^b	20.4 \pm 0.89 ^b	20.8 \pm 0.78 ^b
Permethrin	M	29.0 \pm 1.01 ^a		25.0 \pm 0.57 ^b		21.4 \pm 1.00 ^b		19.9 \pm 1.36 ^b	
25 % CS	F	29.4 \pm 0.92 ^a	29.2 \pm 0.89 ^a	25.0 \pm 1.15 ^b	25.0 \pm 0.81 ^b	21.3 \pm 1.09 ^b	21.3 \pm 0.94 ^b	19.8 \pm 0.42 ^b	19.9 \pm 0.90 ^b
Untreated Control	M	28.7 \pm 2.43 ^a		30.6 \pm 1.91 ^a		30.4 \pm 2.41 ^a		27.3 \pm 2.78 ^a	
0 %	F	28.7 \pm 0.96 ^a	28.7 \pm 1.65 ^a	29.7 \pm 1.65 ^a	30.2 \pm 1.66 ^a	29.2 \pm 2.53 ^a	29.8 \pm 2.31 ^a	26.9 \pm 2.24 ^a	27.1 \pm 2.27 ^a
Means	M	28.7 \pm 1.64 ^a	-----	26.7 \pm 2.66 ^a	-----	23.5 \pm 3.78 ^a	-----	21.4 \pm 3.33 ^a	-----
	F	29.0 \pm 0.85 ^a	-----	26.5 \pm 2.05 ^a	-----	23.4 \pm 3.44 ^a	-----	21.6 \pm 2.95 ^a	-----

M: Male (bull); F: Female (cow); SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension by nanotechnology
 Values followed by the same letters within a column are not significantly differed at 5% according to Duncan's multiple range test.

TABLE 6. Efficacy of novel acaricides and tick's infestation on kidney enzymes, creatinine (Cr) in blood serum of two cattle sexes.

Acaricides	Cattle Sex	Mean \pm SD							
		Week 0	Means	Week1	Means	Week3	Means	Week 6	Means
Acetamiprid	M	2.3 \pm 0.14 ^a		2.1 \pm 0.14 ^{ab}		1.9 \pm 0.21 ^b		1.8 \pm 0.15 ^{bc}	
20 % SL	F	2.0 \pm 0.14 ^a	2.1 \pm 0.20 ^a	1.8 \pm 0.15 ^c	1.9 \pm 0.18 ^b	1.6 \pm 0.15 ^{cd}	1.7 \pm 0.22 ^b	1.5 \pm 0.12 ^{efg}	1.7 \pm 0.19 ^b
Fipronil	M	2.2 \pm 0.38 ^a		2.0 \pm 0.13 ^{bc}		1.8 \pm 0.18 ^b		1.7 \pm 0.22 ^{cd}	
20 % SC	F	2.1 \pm 0.22 ^a	2.2 \pm 0.28 ^a	1.6 \pm 0.10 ^d	1.8 \pm 0.27 ^c	1.4 \pm 0.04 ^e	1.6 \pm 0.23 ^c	1.4 \pm 0.01 ^f	1.6 \pm 0.23 ^c
Lambda-cyhalothrin 10 % CS	M	2.3 \pm 0.10 ^a		2.0 \pm 0.19 ^{bc}		1.7 \pm 0.13 ^{bc}		1.6 \pm 0.13 ^{def}	
	F	2.0 \pm 0.26 ^a	2.1 \pm 0.24 ^a	1.9 \pm 0.14 ^c	1.9 \pm 0.16 ^b	1.6 \pm 0.15 ^{cd}	1.7 \pm 0.15 ^{bc}	1.5 \pm 0.14 ^{fg}	1.6 \pm 0.15 ^c
Permethrin	M	2.2 \pm 0.01 ^a		2.0 \pm 0.03 ^{bc}		1.8 \pm 0.06 ^b		1.7 \pm 0.10 ^{abc}	
25 % CS	F	2.3 \pm 0.08 ^a	2.2 \pm 0.08 ^a	1.6 \pm 0.04 ^d	1.8 \pm 0.20 ^{bc}	1.5 \pm 0.05 ^{de}	1.7 \pm 0.20 ^{bc}	1.4 \pm 0.06 ^f	1.5 \pm 0.15 ^c
Untreated Control	M	2.1 \pm 0.22 ^a		2.2 \pm 0.10 ^a		2.1 \pm 0.05 ^a		1.9 \pm 0.04 ^{ab}	
0 %	F	2.1 \pm 0.32 ^a	2.1 \pm 0.24 ^a	2.2 \pm 0.12 ^a	2.2 \pm 0.10 ^a	2.1 \pm 0.03 ^a	2.1 \pm 0.05 ^a	1.9 \pm 0.02 ^a	2.0 \pm 0.05 ^a
Means	M	2.2 \pm 0.19 ^a	-----	2.0 \pm 0.15 ^a	-----	1.9 \pm 0.16 ^a	-----	1.8 \pm 0.16 ^a	-----
	F	2.1 \pm 0.19 ^a	-----	1.8 \pm 0.26 ^b	-----	1.7 \pm 0.26 ^b	-----	1.6 \pm 0.24 ^b	-----

M: Male (bull); F: Female (cow); SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension by nanotechnology
 Values followed by the same letters within a column are not significantly differed at 5% according to Duncan's multiple range test.

Acaricide residues

Results in Table 7 showed that all acaricides residues were less than the detection limits (ND) in blood and milk samples except fipronil acaricide, which was significantly higher in cow's blood 1.3 µg/l than bulls (ND) after one week of treatment. Similarly, fipronil residues in milk was detected at 2.7 µg/l after 1 week of treatment and then decreased at 1.7 µg/l after 3 weeks. All fipronil residues fell to below detection limits after 3 and 6 weeks in cow's blood and milk, respectively.

Discussion

At the end of the nineteenth century a complex of problems related to ticks and tick-borne diseases of cattle led to get attention on techniques of tick control and lessen injuries of cattle. Recently, Rai and Ingle (2012) reviewed the applications of nanotechnology as the foundation of a new "modern agriculture" to control harmful pests. The study results showed that capsule suspension (CS) formulation by nanotechnology, Lambdacyhalothrin 10 % (CS) and Permethrin 25 % (CS) achieved the most efficacy against ticks compared to conventional acaricides formulations (fipronil 20 % SC and acetamiprid 20 % SL) in this tropical area. Due to decrease in molecules size and enlarged surface area of nanoparticles empowers

easier penetration of the nanoacaricides into tick and enhances its tickicidal activity (Schroff et al., 2003 and Hazra et al., 2017). Moreover, the synthetic pyrethroids like cyhalothrin, cypermethrin, permethrin and deltamethrin have proven to be more effective against ticks and it is a safe group on animals and humans (Msolla et al., 2001; George et al., 2004; Anadon et al., 2013 and Chrustek et al., 2018). Permethrin was the faster acaricide that reached to 100 % reduction of ticks within 3 days. Kumar et al. (2013) reached similar findings, they have observed that, nanopermethrin formulation caused a greater efficacy response at lower concentration. In addition to the protective period was reached to 56 days after permethrin SC treatment without residues either in blood or milk samples. Meanwhile, Kuzuma and Verhage (2006) reported that, the nanopesticides have greater toxicity and many properties; as a result, the required amounts of pesticide utilized could be reduced prompting a decrease in environmental pollution, at last diminishing pest control costs. On the other hand, fipronil acaricide was highly efficacy (97.3%) following 24 hours of treatment. Similar results were attained by Cruthers et al. (2001) who found that, the speed of kill of fipronil, applied topically, was 100% against *R. sanguineus* ticks between 24 and 48 hours after treatment. However, it achieved the minimum

TABLE 7. Acaricides residues detected in cattle's blood and cow's milk samples at various post-treatment times.

Acaricides	Cattle Sex	Mean concentration (µg / l) ± SD							
		cattle's blood				cow's milk			
		Week 0	Week1	Week3	Week 6	Week 0	Week1	Week3	Week 6
Acetamiprid 20 % SL	M	ND	ND	ND	ND				
	F	ND	ND	ND	ND	ND	ND	ND	ND
Fipronil 20 % SC	M	ND	ND	ND	ND				
	F	ND	1.3±0.4	ND	ND	ND	2.7±0.2	1.7±0.2	ND
Lambda-cyhalothrin 10 % CS	M	ND	ND	ND	ND				
	F	ND	ND	ND	ND	ND	ND	ND	ND
Permethrin 25 % CS	M	ND	ND	ND	ND				
	F	ND	ND	ND	ND	ND	ND	ND	ND
Untreated Control 0 %	M	ND	ND	ND	ND				
	F	ND	ND	ND	ND	ND	ND	ND	ND

M: Male (bull); F: Female (cow); SL: soluble concentrates; SC: suspension concentrates; CS: capsule suspension by nanotechnology. ND: Not detected under the limit of detection.

protective period of 42 days with the presence of residues in the blood and milk samples under the maximum residue limit (MRL, 0.008 mg/l in milk).

The parasitic burden on cows was significantly higher than bulls in pre-treatments. Gharbi et al. (2014) reached similar findings, they have observed that female cattles were more infested than males. On the other hand, the opposite trend was recorded after reducing the tick load and animal healing. These results were agreed with the observations of Chartier et al. (2000). This may be due to an increase in the amount of carbon dioxide gas produced by increase the metabolism and feeding rate of treated animals, which may be greater in bulls than cows, hence attracts more ticks. Similar results were attained by Musa et al. (2014) who demonstrated that, male bovines emit much more CO₂ gas than the female, which explains the high parasitic load. However, Flach et al. (1995) did not observe any relation between immature tick burdens and sex of the cattle hosts. This difference is possibly attributed to the body size and the different quantities of attractive chemicals such as carbon dioxides (Donzé et al., 2004) or genetic factors of the host (Yessinou et al., 2018). The amount of carbon dioxide (CO₂) emitted is the first deciding factor to attract the ticks to their hosts (Wanzala et al., 2004).

Ticks causes stress and weakens the host's immune responses which affect the performance of the animals and causes reduced feed intake, so increasing body weight loss (Jonsson, 2006^b). The significant difference in weight loss obtained in the first period of the study between the untreated cattle (Control) that has stress by tick infestation only and the treated cattle which may be having stress by tick infestation and acaricides effects together. Another factor to note in this study is the difference in weight gain achieved between treated and untreated animals. The results suggest that at least a part of the increased weight gain observed in the treated cattle was due to the reduction in physiological stress often associated with abundant tick infestation on the cattle (Davey et al., 1999). These results agree with the findings of Remington et al. (1997) who found that the increasing weight gain were obtained from treated animals against ticks. Whereas previously infested animals do not grow significantly faster than animal kept tick-free (Seebeck et al. 1971; Jonsson, 2006^a and Hurtado et al., 2018). There was a difference in the response of recovering

of the lost weight within intervals times, but in the end, there were no significant differences in weight gain for all acaricides treatments, which is associated with the evanescence of acaricidal effects and tick infestation.

Furthermore, cattle under the most stressful of tick infestation were suffered from high levels of liver and kidney enzymes than normal values. The normal ranges of AST and ALT activities (U/l) are 19.2 to 84.90 and 4.2 to 29.7, respectively recorded previously in cattle by Stojevic et al. (2005). The significant decreasing of AST and ALT with the advancement of experimental period may be due to a decrease in the numbers of ticks on animals as a result of using different acaricides in comparison with untreated animals. The present results agree with Laiblin et al. (1978), Omer et al. (2003), Sandhu et al. (1998) and lotfollahzadeh et al. (2012). Also, the declining of kidney functions (BUN and Cr mg/dl) may be due to a more positive effect of these treatments, normal protein metabolism reflected on improvement of body weight by using different acaricides treatments as a result of decrease the numbers of ticks on treated animals in comparison with untreated (Kerr, 1989 and Omer, et al., 2003).

The controlled release of active ingredient was the main goal of encapsulated formulations by nanotechnology and to reduce the amount of pesticides residue in environment (Ali et al., 2014 and Cicek & Nadaroglu, 2015). In comparison results of the acaricide formulations detected in blood and milk samples it was showed that permethrin 25 % CS and lambada-cyhalothrin 10 % CS weren't detected in all samples due to leave minimum residues as a result of which reduce the doses rate and repeated of applications (Rudzinski et al., 2002; and Roy et al., 2014). On the other hand, Fipronil 20 % SC residues were detected in cow's blood and milk samples. but they were found lower than European maximum residues level (MRL= 8 µg /l). Similarly, Faouder et al. (2007) and Bedi et al. (2015) were reported that fipronil pesticide is used as flea and tick sprays for domestic animals hence it was excreted in milk.

Conclusion

In conclusion, the capsule suspension (CS) formulation by nanotechnology, permethrin 25 % CS and lambada-cyhalothrin 10 % CS achieved the highest efficacy 97.4 % and 95.6 %, respectively against cattle ticks up to 70 days post-treatment without any detection of residues

in blood and milk samples. Additionally, they didn't impact liver and kidney function enzymes. Also, permethrin 25 % CS treatment had a highly beneficial impact on weight gain production. Eventually, controlled release formulations (CRF) by nanotechnology improved the efficacy of acaricides with minimizing their residue in animal products, and reducing risks for human, animals, and environmental health in tropical areas.

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Conflict of Interest

The authors declare no competing interests regarding the publication of this paper.

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المبيدات الأكاروسية الجديدة بتكنولوجيا النانو ضد قراد الماشية وتأثيرها على الأداء الفسيولوجي والإنتاجي

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^٣المعمل المركزى لتقدير متبقيات المبيدات والعناصر الثقيلة فى الأغذية - المركز القومى للبحوث - مصر

أجريت تجربة حقلية لتقييم فعالية جُهيزة الكبسولات المعلقة (CS) بواسطة تقنية النانو والمبيدات التقليدية ضد قراد الماشية (*Hyalomma marginatum*) وتأثيرها على وزن الجسم وأنزيمات دم ماشية الأبردين أجلس. تم تقدير بقايا هذه المبيدات في دم وحليب الحيوان. قسم ثلاثون ماشية مصابة بطريقة عشوائية الى خمس مجموعات في كل منها ختوى على ٣ ثيران و ٣ أبقار بناءً على متوسط عدد القراد. فأظهرت النتائج أن مبيد بيرميثرين ٢٥٪ كبسولات معلقة ولمباداسيهالوثرين ١٠٪ كبسولات معلقة الأكثر فاعلية ضد القراد (٢,٧ و ٣,٨ قراد / حيوان . على التوالي) مقارنةً بمبيد فيبرونيل ٢٠٪ معلق مركز و أسيتامبريد ٢٠٪ مركز قابل للذوبان (٨,٣ و ١,٣ قراد / حيوان . على التوالي) بعد ٧٠ يوما من المعاملة. حقق بيرميثرين ٢٥٪ كبسولات معلقة السيطرة بنسبة ١٠٠٪ ضد الإصابة بالقراد بعد ٣ أيام من العلاج والحفاظ على هذه النسبة لمدة ٥٦ يوما دون أثر لمتبقيات في عينات الدم والحليب. وعلى العكس، تم اكتشاف بقايا مبيد فيبرونيل في دم ولبن الأبقار (١,٣ و ٢,٧ ميكروجرام / مل . على التوالي) بعد أسبوع من العلاج بينما لم يتم الكشف عنه في دم الثيران. والتي أنخفضت تدريجيا إلى أقل من حدود الكشف بعد ٣ و ٦ أسابيع على التوالي. زاد وزن جسم الحيوان معنويا . بالإضافة إلى انخفاض وظائف الكبد والكلى إلى المستوى الطبيعي في جميع الحيوانات المعالجة. و أخيرا، يمكن استخدام البيرميثرين و لمباداسيهالوثرين بتجهيزة CS كمبيدات فعالة وكبديل آمن في استراتيجية التحكم في القراد بالمناطق المدارية.