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Animal Reproduction Research Institute,
El-Haram, Giza, Egypt.

EFFECT OF IVERMECTIN ON THE REPRODUCTIVE PERFORMANCE IN RAMS

(With 3 Tables and 3 Figures)

By

MARY, G. ABD EL-MALAK; H.M. HASAAN; MAGDA A. EL-SHELTAWI and G. ABD EL-MALAK

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تاثير عقار الايفرميكتين على الكفاءة التناسلية فى الكباش

مارى جاد عبد الملاك ، هانى محمد حسن ، ماجد احمد الشلتاوى ، جرجس عبد الملاك

استخدم فى هذه الدراسة خمس كباش جيده يبلغ عمرها حوالى اربعة اعوام حقنت بعقار الايفرميكتين تحت الجلد بجرعة تبلغ ٢رمجم/كجم من وزن الحيوان وقد تم تجميع عينات سائل منوى محكمة من كل حيوان مرة اسبوعيا لمدة اربع اسابيع على التوالى قبل الحقن على انه بعد الحقن تم تجميع عينات السائل المنوى مرة اسبوعيا لمدة عشرة اسابيع متتالية وبعد التجميع مباشرة تم تقيم صفات السائل المنوى مثل حجم القذفة (سم^3) ، تركيز الحيامن فى سم^3 ، نسبة الحركة الامامية ، نسبة الحى والاشكال الشاذة . هذا بالاضافة الى قياس بعض الدوال التناسلية لكل حيوان على حدة وهى محيط غشاء الصفن (سم) وزمن الوثبة (بالثانية) وقد تم ايضا قياس درجة حرارة كل حيوان على مدى التجربة مع ملاحظة اى علامات للالتهاب على الحيوان . ولقد اسفرت النتائج على ان عقار الايفرميكتين قد اثر على حجم القذفة حيث أنها زادات معنويا في الفترتين الأولى والثانية بعد الحقن ثم قلت حتى وصلت إلى المستوى الطبيعى قبل الحقن (٧٤ر١ ± ١ر بالمقارنة ٤٣ر٢ ± ٢١ر٠ ، ٢٥ر٢ ± ١٢ر٠ ، ١٧ر١ ± ١٤ر٠) وكذلك أيضا كان نفس التأثير على تركيز الحيامن (٣٤٦٧ ±٦ر٢١٨ بالمقارنة ٣٦١٠ ± ٩٥ر٦٦٣ ، ٣ر٣٧٠٥ ± ٤ر١٩٥ ، ٣٢٨٨ ± ٤ر٣٠٩ × ١٠^6/ مللى) كما لوحظ نفس التأثير على نسبة الاشكال الشاذة التي زادات طوال فترة التجربة (٨٥ر١ ± ٢٦ر٠ بالمقارنة ٧٣ر٦ ± ٨٨ر٠ ، ٩٣ر٨ ± ٤٨ر١ ، ٨٥ر٤ ± ٨٦ر٠ %) على الترتيب . بينما قلت نسبة الحى معنويا خلال فترة التجربة (٧٥ر٨٧ ± ٧١ر١ بالمقارنة ٣٣ر٨٢ ± ٨٥ر١ ، ٦٠ر٨٠ ± ٩٧ر٢ ، ٥٠ر٨٠ ±١٠٧٢ %) وبالنسبة لمحيط غشاء الصفن فقد زاد معنويا حتى نهاية الفترة الثانية ثم قل في الفترة الثالثة من الحقن (٣٥ر٣١ ± ٤٩ر٠ بالمقارنة ٢ر٣٣ ± ٥٧ر٠ ، ١٥ر٣٣ ± ٥٧ر٠ ، ٣ر٣٢ ± ٥٧ر٠ سم) . ومن ناحية أخرى لم يؤثر عقار الايفرميكتين على نسبة الحركة الأمامية وزمن الوثب ودرجة الحرارة وفي نفس الوقت

قد تأثرت الاختلافات الفردية للكباش بعقار الايفرميكتين تأثيرا معنويا عاليا خاصة فى تركيز الحيامن ومحيط غشاء الصفن علاوة على ذلك قد وجد تداخل معنوى واضحا بين المعالجة بالايفرميكتين والاختلافات الفردية للكباش فى تركيز الحيامن وارتفاع درجة الحرارة . كما لوحظ وجود التهاب واضح فى منطقة مابين الفخذين من بداية الفترة الأولى حتى نهاية الفترة الثانية بعد الحقن . لذلك يمكن استخدام عقار الايفرميكتين بامان كمضاد للطفيليات للكباش المستخدمة فى التلقيح ولكن اثناء هذه الفترة يتم وضع هذه الكباش تحت الملاحظة.

SUMMARY

Five rams aged 4 years were used in this study. Semen was collected weekly from each ram for successively 4 weeks as control, then Ivermectin was injected S/C with therapeutic dose (0.2 mg/ kg body weight). After one week from injection semen samples were collected from each ram once weekly for 10 weeks. Semen was evaluated for volume, sperm cell concentration, percentage of individual motility, percentage of live spermatozoa and percentage of abnormal spermatozoa. Testicular circumference, reaction time and body temperature were recorded. In addition any signs of inflammation were observed. The obtained results showed that semen volume increased significantly in the 1st and the 2nd period of Ivermectin injection (1.47±0.1 VS 2.43±0.21 and 2.25 ±0.12 ml) after that it reduced nearly to normal level before treatment (1.17±0.14ml). The same trend was observed on sperm concentration where the increase began at the 1st period of treatment till the end of the 2nd one (3467±218.6 VS 3610±663.95 and 3705.3±195.4x10^6/ml) then reduced at the 3rd period of treatment (3288±309.4x10^6/ml). Also, the percentage of abnormal spermatozoa increased significantly ($P<0.01$) specially coiled tail all over the periods of treatment (1.85±0.26 VS 6.73±0.88, 8.93 ± 1.48 and 4.85 ±0.86 %).While, the percentage of live spermatozoa reduced significantly ($P<0.01$) through the periods of treatment (87.75±1.71 VS 82.33±1.85, 80.60 ±2.97 and 80.5 ±1.72 %). The testicular circumference increased significantly ($P<0.01$) till the end of the 2nd period of treatment then declined in the 3rd one (31.35± 0.49 VS 33.2±0.57, 33.15±0.57 and 32.3±0.57 cm. respectively). On the other hand, Ivermectin treatment doesn't revealed any significant effect on percentage of individual motility, reaction time and the body temperature. On the same line, rams differ significantly ($P<0.01$) in their response to ivermectin on semen volume, sperm concentration and testicular circumference. Furthermore, interaction between periods of treatment and ram individual variation

was pronounced significantly in sperm concentration and rise in body temperature. Also, local inflammation developed during the 1st period of treatment on the perineal as well as perpetual regions in all tested rams and disappear after the end of the 2nd period of treatment. So, Ivermectin can be used safely as antiparasitic drug for sheep but during the treatment period rams can be used for breeding under restricted observations.

Key Words: *Ivermectin, Reproductive, Performance,Rams*

INTRODUCTION

Ivermectin was the non proprietary commercial name of 22,23 dihydroavemectin B, which proved to be potent as it contain 5- hydroxy group (Fisher and Morzik , 1989), a fact that lead to the wide use of the compound as antiparasitic drug for sheep (Hotson, 1983), goat (Zeybek, 1986), swine (Becker, 1986) and dog (Kobayshi et al., 1988).The relatively longer half life (7.4 days) reported by Prichard et al. (1985), necessitate studying the side effect of the drug on the different physio-chemical events in horses (Campbell and Benz, 1984 and Herd and Kociba, 1985), cattle (Leaning et al., 1983 and Brem and Bulman , 1986), sheep (Hotson, 1983) and goat (Njanja et al., 1985).

Also the teratological effect of Ivermectin during the different periods of gestation were recorded in cattle by Leaning et al. (1983), ewes by Hotson (1983) and in sow by Brokken et al. (1983), they stated that Ivermectin administration had no adverse effect on the dam or the fetus during gestation.

Furthermore it was proved that Ivermectin therapy did not affect the breeding performance of bulls (Leaning et al., 1983) rams (Schroder et al., 1986) and Boars (Brokken et al., 1983). Although Ali et al., (1988) stated that Ivermectin was not toxic as a single dose but repeated doses may be lethal, Schroder et al. (1986) and Harvey (quoted by Pulliam and Preston, 1986) found no lethality to Ivermectin when it is administrated in repeated doses on the reproductive potential of rams, a fact that needs further investigation.

The present work aimed at elucidating the effect of Ivermectin on the reproductive performance of ram after a single dose.

MATERIALS and METHODS

Sexually mature, clinically healthy five rams aged 4 years were used. They were kept at the experimental farm of Animal Reproduction Research Institute (ARRI). Semen Samples were collected using artificial vagina once weekly, where first and second ejaculates were pooled together from each ram. Semen samples were collected successively for 4 weeks, from each ram, before administration of Ivermectin and served as a control samples. At the end of the 4th week animals were injected subcutaneously with a therapeutic dose (0.2 mg/kg B.W) of Ivermectin (Ivomec®, Merk Sharp and Dohme. USA). After one week from injection semen samples were successively harvested from each ram weekly for 10 weeks. For the bioexponantial decay of Ivermectin in sheep blood plasma (Lo et al., 1985) and the longer half life reported by Prichard et al., 1985), the post administration time was divided into three periods, the first one was extended from the first to the third week after injection (three collections with one week interval). The second period extended from the fourth till the sixth week after injection (three collections with one-week interval), while the last period representing the last four weeks post treatment (four collections with one-week interval).

Immediately after collection, semen samples were subjected to the conventional methods of evaluation (Salisbury et al., 1978). Volume, Sperm cell concentration, percentage of individual motility, percentage of live spermatozoa (Campbell et al., 1956) and percentage of abnormal spermatozoa (Bloom, 1983). During the whole experiment testicular circumference, reaction time (Marrow, 1986) body temperature and any sign of inflammation were recorded. Data was subjected to statistical analysis according to Senedecor and Cochran (1982).

RESULTS

It is clear from the present results that Ivermectin administration to rams affects significantly ($P<0.01$) semen volume ($F = 11.16^{++}$), sperm concentration ($F = 4.89^{++}$), percentage of live spermatozoa ($F = 3.23^{++}$) and percentage of abnormal spermatozoa ($F = 9.55^{++}$). Also, the difference between rams under the effect of Ivermectin is very pronounced ($P<0.01$) on semen volume ($F = 8.31^{++}$) and sperm concentration ($F = 13.53^{++}$) .In addition, no detectable significant interaction between rams and periods of treatment was observed. On the

other hand, Ivermectin treatment doesn't revealed any significant effect on percentage of individual motility (F = 0.16). Figures gathered in Table (1) indicated that semen volume increased significantly in the 1st period of treatment (1.47±0.1 VS 2.43±0.21ml) that a phenomenon persisted till the end of the 2nd period of treatment (2.25 ±0.12ml) after that it reduced nearly to normal level before treatment (1.17±0.14ml). The same trend was observed on sperm concentration where the increase began at the 1st period of treatment (3690±196.0 X 10^6/ml) and continued till the end of the 2nd period of treatment (3705.3 ±195.40x10^6/ml) then declined nearly to the figures that obtained before treatment (3288±309.4 VS 3467±218.6 X10^6/ml) .At the same time, percentage of individual motility reduced non significantly post treatment, while significant reduction ($P<0.01$) was obtained in the percentage of the live Spermatozoa until the end of the experiment (87.75±1.71 VS 82.33±1.85, 80.60 ±2.97 and 80.5 ±1.72%). Also, S/C injection of Ivermectin provoked a significant increase ($P<0.01$) in the percentage of abnormal spermatozoa specially coiled tail. This increase was observed at the 1st period of treatment (6.73±0.88%) till the end of the 2nd period of treatment (8.93 ± 1.48%) and then reduced slightly till the end of the experiment (4.85 ±0.86 %) if compared to that observed before treatment (1.85±0.26%). It was proved from the present result that testicular circumference exhibited a significant ($P<0.01$) difference through periods of treatment ($F= 6.64^{++}$) and between rams ($F= 24.42^{++}$), In spite of there is no significant interaction between them. (F= 1.81). The significant increase in testicular circumference up to 1.45 cm was determined at the 1st period of treatment and sustained until the end of the 2nd period of treatment (33.2±0.57 and 33.15±0.57 cm. respectively). At the end of the 3rd period of treatment it was reduced about 0.8 cm in diameter (Table 2).

On the other hand, the effect of Ivermectin on reaction time didn't evoke any significant difference between either periods of treatment or between rams (F = 1.56, 0.99 respectively). None of the interaction between them proved to be significant (F= 1.81) (Table 2).

Table (3) revealed that Ivermectin didn't effect a body temperature of ram either during periods of treatment or between rams (F= 1.00, 0.93 respectively). However the interaction between them was proved to be highly significant ($F= 3^{++}$). Range between Maximum and minimum body temperature was (39.83- 39.23 °C). It was observed through the periods of the study that local inflammation was developed during the 1st period of treatment on the perineal as well as perpetual

regions in all tested rams and disappear after the end of the 2nd period of treatment.

The effect of Ivermectin on semen characterstics, reproductive characteristics and body temperature were demonstrated in figures 1, 2 and 3 respectively.

DISCUSSION

In line with the scanty reports on the effects of Ivermectin on the reproductive potential of rams (Schroder et al., 1986). The present study revealed that Ivermectin affects significantly ($P<0.01$) semen volume, Sperm cell concentration, percentage of live spermatozoa, percentage of abnormal spermatozoa and testicular circumference through the periods of treatment, also rams differs significantly ($P<0.01$) in their response to Ivermectin on semen volume, sperm concentration and testicular circumference. Furthermore interaction between periods of treatment and rams individual variations was pronounced significantly ($P< 0.01$) in sperm concentration and the rise of the body temperature.

In contrast with the present study Harvey (quoted by Pulliam and Prestom 1986) stated that administration of Ivermectin subcutaneously to rams at 300 mg / kg B.W twice with a 7-day interval had no adverse effect on semen volume, apparent wave motion, progressive motility, sperm concentration, percent of dead spermatozoa and cytological examination. Furthermore Schroder et al. (1986) found that no adverse effect on semen volume, density, color, motility, pH, percentage of live sperm and sperm morphology on repeated treatment with Ivermectin at 400 mg /Kg B.W at 21 days intervals. The possible explanation of the increased semen volume in the present study is the expected congestion of the accessory sex gland after Ivermectin injection. This finding agree with Zaied (1995) who revealed that some alterations in the male rabbit reproductive organs after Ivermectin injection represented by congestion and edema of the prostate gland, which may affect the environment and medium necessary for the sperm function. A fact that might explain the significant decrease in percentage of live spermatozoa, the increase percentage of abnormal spermatozoa specially coiled tail and the increased testicular circumference in the present study may be due to the persistent harmful effect of Ivermectin residue in the testis fat (Jacob et al., 1983) resulting in interstitial edema, giant cell formation with necrosis of spermatogenic cell accompanied by eosinophilic debris inside

the seminefrous tubules (Zaied, 1995) as well as the detected local inflammation in the preineal and perpetual regions.

In spite of the recorded decrease in serum level of FSH, LH and the possible decrease in testosterone level in rabbit. (Jacob et al. 1983, and Zaied , 1995). The present study didn't detect any change in the reaction time either through the periods of treatment or between rams which might reflect the stability of the endocrine system of rams against Ivermectin administration. This finding may be due to the result proved by Zaied (1995) who reported that serum cholesterol increased after Ivermectin injection to rabbit at level of 0.3 mg /Kg B.W, as it would be known that cholesterol is essential for the synthesis of sex hormone (Strand, 1988).

Furthermore Ivermectin administration didn't rise the body temperature of the treated rams in the present study, which contrast the recorded side effect of the drug (Hotson, 1983, Washko and Hotson, 1983).

It could be suggested that the difference in response of the male reproductive system to Ivermectin in the present study and others might be due to species differences, breed, management, route of drug administration and doses as well as the differences in metabolism of Ivermectin in different species (Campbell, 1989 and Zaied, 1995).

On the view of the present results, and the relatively low number of the tested rams (5 rams) . Also, the possible significant effect of individual variation under the effect of the drugs on the reproductive potentials, Ivermectin can be used safely as antiparasitic drug for sheep but during the of treatment periods (10 weeks) rams can be used for breeding but under restricted observations. However, further investigation should be needed to detect the effect of Ivermectin on conception rate.

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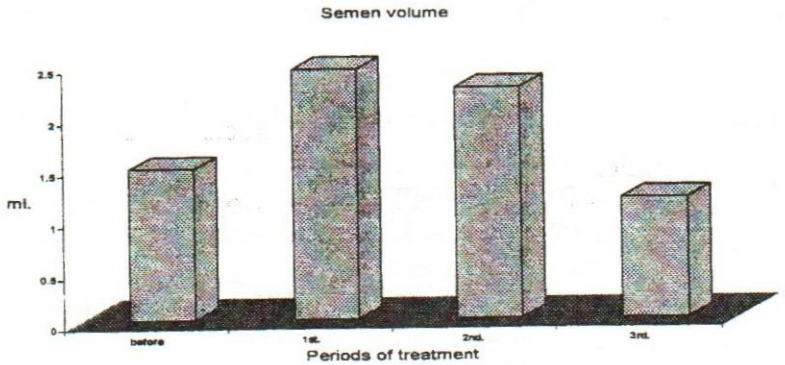
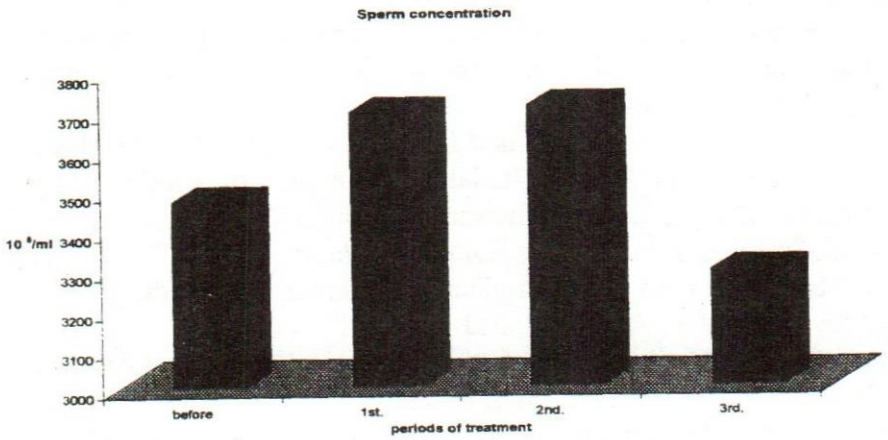




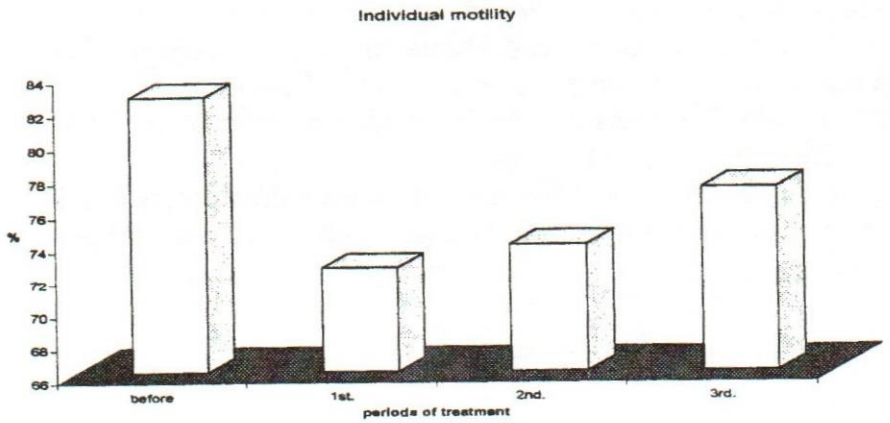
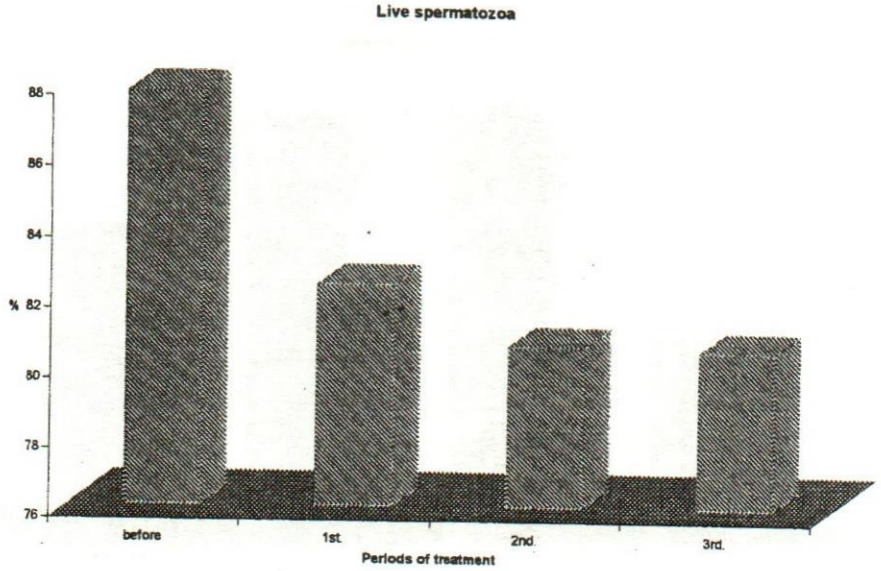
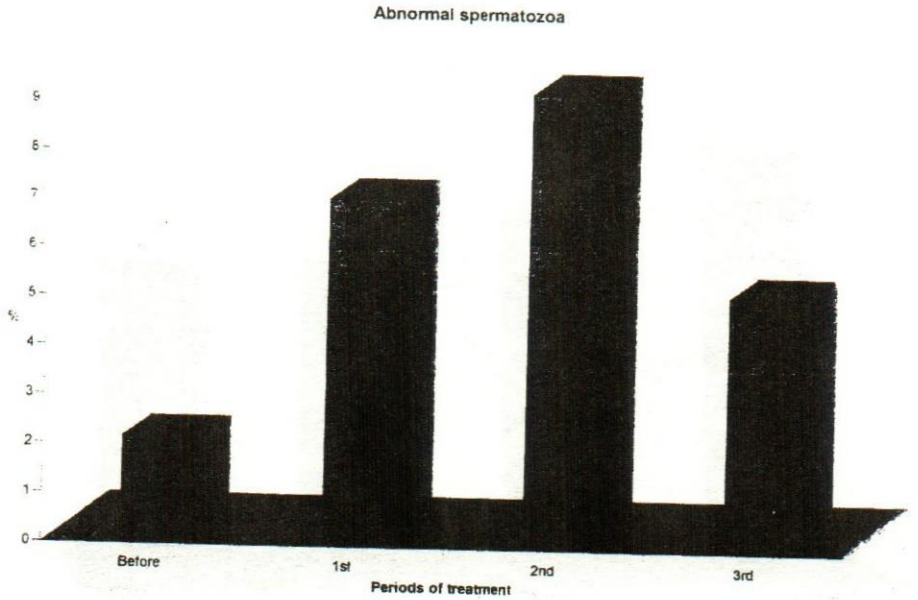
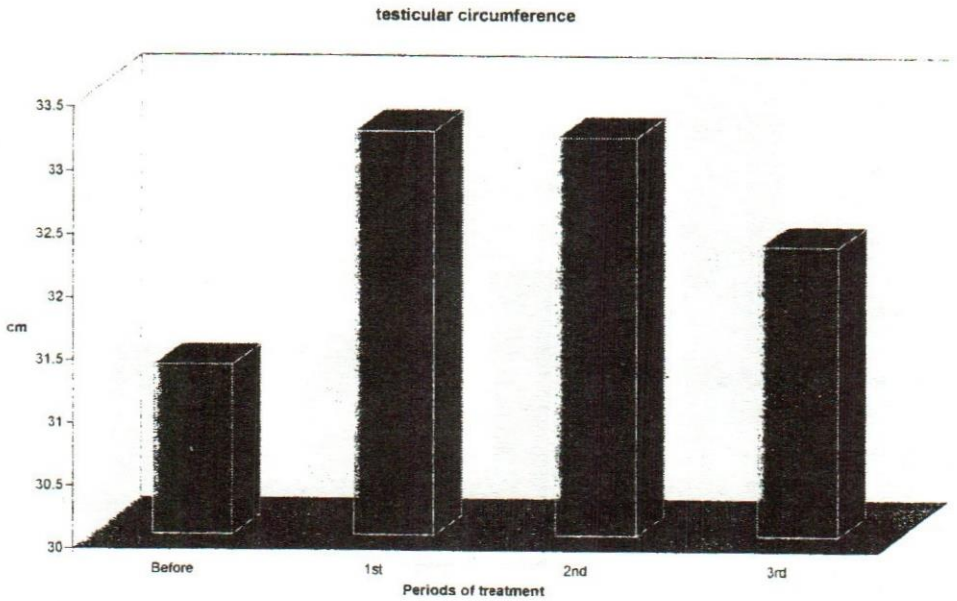


Fig. (1) : Effect of Ivermectin on semen characteristics of rams





Cont. Fig(1) : Effect of Ivermectin on semen characteristics of rams



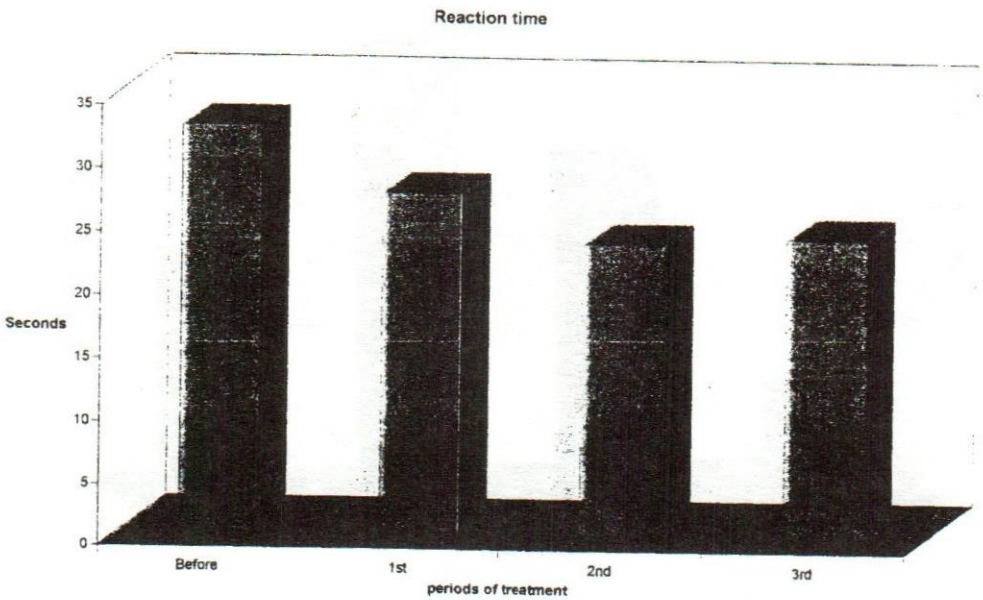


Fig.(2) Effect of Ivermectin on reproductive charecteristics of ram

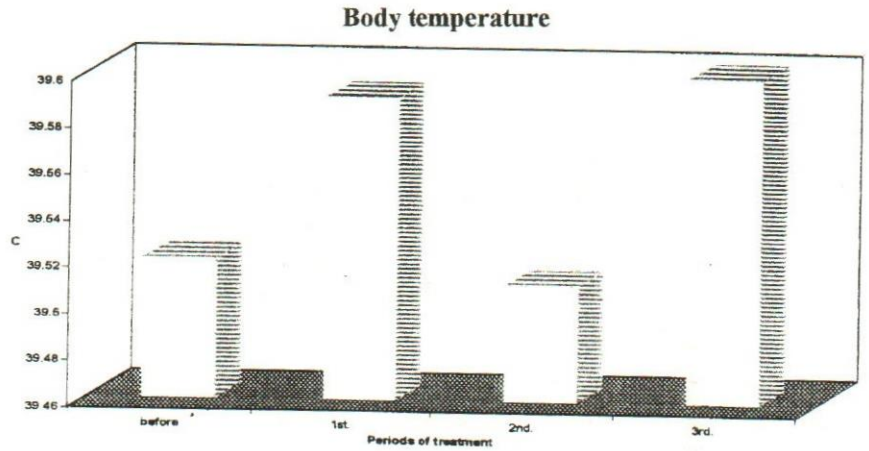


Fig. (3) Effect of Ivermectin on body temperature of rams

TABLE (1) : Effect of Ivermectin administration on ram semen characteristics (Mean ± S.E) .

Semen Characters	Ram No	Before Treatment	Periods of treatment /weeks			Over all Mean
			First	Second	Third	
Volume (ml.)	1	1.88±0.13	2.90±0.58	2.13±0.31	2.33±0.3	2.26±0.18 ^{a}
	2	1.65±0.20	2.27±0.43	2.75±0.43	1.77±0.23	2.12±0.19 ^{a}
	3	1.60±0.14	2.77±0.67	2.70±1.35	1.70±0.15	2.19±0.21 ^{a}
	4	1.43±0.15	2.50±0.29	2.38±0.24	2.0±0.29	2.05±0.12 ^{a}
	5	0.78±0.10	1.70±0.17	1.38±0.15	1.17±0.16	1.23±10.1 ^{b}
Over all mean		1.47±0.1 ^{A}	2.43±0.21 ^{B}	2.25±0.12 ^{B}	1.17±0.14 ^{A}	1.97±0.09
Sperm Concentration (x 10^{6} /ml.)	1	3030±479.55	4600±138.56	3433.33±81.92	319(±963.52	3498.57±322.82 ^{ac}
	2	2330±377.49	3150±340.64	4100±470.32	2345±483.35	2889.29±273.10 ^{b}
	3	4190±220.38	3330±317.54	3806±318.29	3345±594.27	3682.14±208.85 ^{c}
	4	4370±277.67	3760±196.30	3273.33±878.21	3800±223.42	3841.43±279.09 ^{ac}
	5	3415±244.59	3610±663.95	3913.33±229.06	3760±729.09	3662.14±237.09 ^{c}
Over all mean		3467±218.60 ^{AB}	3690±196.08 ^{BA}	3705.3±195.4 ^{C}	3288±309.4 ^{CA}	3514.41±122.57
Percentage of Individual Motility (%)	1	85.00±.04	66.67±1.67	78.33±4.41	73.75±2.39	76.43±2.19
	2	77.5±2.23	76.67±1.67	75.0±5.0	71.25±1.25	75.0±1.48
	3	87.5±1.44	76.67±1.67	75.0±2.87	81.25±1.25	80.71±1.52
	4	68.25±3.75	76.67±4.41	71.67±10.93	80.0±2.04	79.29±2.82
	5	76.25±2.39	65.0±2.87	68.33±8.33	78.75±2.39	72.86±2.38
Over all mean		82.5±1.52	72.33±1.75	73.67±2.78	77.0±1.10	76.86±0.98
Live (%)	1	87.25±3.33	82.33±0.33	87.67±4.33	78.0±6.96	83.64±2.41
	2	86.25±4.17	90.33±2.03	87.67±2.60	77.0±3.08	84.79±2.04
	3	89.75±1.97	83.33±1.45	79.67±2.96	84.75±2.02	84.7±1.38
	4	86.25±7.25	83.67±4.33	76.67±8.09	83.0±1.47	82.71±2.69
	5	89.25±1.93	72.0±2.87	71.33±10.35	79.75±3.81	79.0±3.02
Over all mean		87.75±1.71 ^{A}	82.33±1.85 ^{B}	80.60±2.97 ^{B}	80.5±1.72 ^{B}	82.99±1.06
Percentage of Abnormal Spermatozoa	1	1.5±0.65	5±2.31	8.67±4.91	5.5±2.5	4.93±1.32
	2	1.25±0.48	3.33±0.33	8.67±0.33	4.5±2.06	4.. 21±0.91
	3	2.0±0.1	9±2.89	10.67±1.86	9.25±0.85	6±1.20
	4	2.0±0.91	9±0.01	10.33±4.37	6.25±2.98	6.50±1.42
	5	2.5±0.29	7.33±0.89	6.33±5.3	3.75±1.49	4.71±1.19
Over all mean		1.85±0.26 ^{B}	6.73±0.88 ^{BCD}	8.93±1.48 ^{CB}	4.85±0.86 ^{DB}	5.27±0.54

Means with different superscripts A,B.. for Rows and a,b .. for column are significantly different at P<0.01 .

(Table 2): Effect of Ivermectin administration on some reproductive characteristics. (Mean ± S.E)

Reproductive Characters	Ram No	Before Treatment	Periods of treatment /weeks			Over all Mean
			First	Second	Third	
Testicular Circumference (Cm)	1	34.25±0.48	36.50±0.87	35.7±0.48	35.5±0.76	35.43±0.35^{a}
	2	32.25±0.85	33.0±0.58	32.5±0.87	31.6±0.87	32.41±0.36^{bc}
	3	30.50±0.87	33.50±0.29	34.25±0.63	33.16±0.92	32.70±0.53^{bc}
	4	30.5±0.87	30.5±0.58	33.5±0.20	30.97±0.55	31.46±0.45^{abd}
	5	29.25±0.48	32.5±0.87	29.7±1.44	30.33±0.67	30.32±0.55^{dc}
Over all mean		31.35±0.49^{A}	33.2±0.57^{B}	33.15±0.57^{B}	32.3±0.57^{A}	32.48±0.28
Reaction Time (Seconds)	1	38±5.46	20±5.77	25±4.51	47.25±3.17	34.0±5.07
	2	28.2±6.51	17±7.51	42.33±6.99	19.25±8.08	26.36±6.45
	3	38.5±2.6	22.33±4.33	120±3.6	15.5±2.9	22.79±3.25
	4	30±9.56	45±8.66	24±3.79	13.87±3.43	27.32±1.38
	5	31±6.66	30.67±0.67	12.33±4.63	25.5±9.37	24.5±3.68
Over all mean		32.2±2.78	27±3.54	23.13±5.65	23.68±4.44	26.99±2.09

Means with different superscripts A.B. for rows and a.b... for column are significantly different at P<0.01

(Table 3) :Effect of Ivermectin administration on the rise of the rams' body temperature (°C) (Mean ± S.E.)

Ram No	Before Treatment	Periods of treatment /weeks			Over all Mean
		First	Second	Third	
1	39.33±0.12	39.53±0.09	39.67±0.09	39.83±0.03	39.59±0.07
2	39.55±0.10	39.53±0.09	39.4±0.1	39.58±0.05	39.52±0.04
3	39.63±0.22	39.23±0.09	39.57±0.15	39.67±0.08	39.45±0.08
4	39.48±0.14	39.83±0.09	39.30±0.01	39.40±0.09	39.49±0.07
5	39.6±0.14	39.8±0.13	39.40±0.09	39.53±0.03	39.62±0.05
Over all mean	39.52±0.06	39.59±0.07	39.51±0.05	39.6±0.04	39.55±0.03