Evaluating the Efficiency of Various Treatment Methods in Cattle Cutaneous Papillomatosis

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Summary
In this study, we compared the effectiveness of various methods used in the treatment of cattle with cutaneous papillomatosis. For this, Ivermectin, *Tarantula cubensis* extract, levamisole, autovaccine, and a combination of *T. cubensis* extract + levamisole was administered to the animals. The animals were divided into six equal groups. Animals in the control group (n = 10) did not receive any treatment. The animals in the experimental group were administered Ivermectin (three times a week, n = 10, subcutaneous, (SC)), *Tarantula cubensis* extract (twice a week, n = 10, SC), autologous vaccine (three times at 10-day intervals, n = 10, SC), levamisole (twice at one-week intervals, n = 10, intramuscular (IM)), and levamisole + *Tarantula cubensis* extract (concurrently). All animals used in the study were monitored for three months at an interval of 15 days. No regression was detected in the papillomas of the control group animals, but recovery was recorded in animals treated with ivermectin at a rate of 70% (7/10), while it was 60% (6/10) in those treated with *T. cubensis* extract, 100% (10/10) in those treated with autovaccine, 50% (5/10) in those treated with levamisole, and 90% (9/10) in those treated with the combination of *T. cubensis* extract + levamisole. Significant differences were found between the control group and all treatment groups. Recovery mostly occurred within 45–60 days ($P < 0.05$) The five treatment modalities applied for the treatment of bovine cutaneous papillomatosis were statistically evaluated and all methods of treatment were effective at different rates. The most precise and effective treatment method was the autovaccine.

Introduction

Bovine papillomavirus (BPV) infections are among the most common global health problems in large cattle farms. The virus causes chronic tumours (benign and malignant) and contagious diseases, especially in breeding farms where numerous animals live together and cause malnourishment, stress, immune depression and economic losses in such affected animals (Tan *et al*. 2012, Ugochukwu *et al*. 2019). Papillomavirus forms lesions characterized by cutaneous and mucosal fibropapillomas, papillomas, and neoplasia (Maclachlan *et al*. 2011, Araldi *et al*. 2017). Papillomavirus was previously placed in the Papoviridae family but was later placed in a different family called Papillomaviridae.

Papillomaviruses are strain or tissue-specific, inter-host cross infections have also been reported in various studies. This virus causes diseases in different ways in wild or domestic ruminants and leads to high morbidity (Maclachlan *et al*. 2011). The virus infects by direct contact. The risk of a papillomavirus infection increases though iatrogenic mistakes during castration, injection, ear tag insertion, cauterisation, due to contaminated forage and equipment, heredity, hormonal imbalance, malnutrition, hygiene deficiency, non-optimized milking machines, and poor housing conditions. Stress and immune depression caused by these conditions are the primary reasons for the occurrence of papillomatosis and other important

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infectious diseases (Maclachlan *et al*. 2011, Daudt *et al*. 2018, Ugochukwu *et al*. 2019).

Cutaneous papillomas are identified as benign proliferative neoplasia whose etiology and pathogenesis are complicated. They occur invarious forms in cattle, including bovine papillomavirus (BPV) filiform, peduncular, and squamous papillomas (Jelinek and Tachezy 2005, Lunardi *et al*. 2016). The most common type of peduncular form is the 'cauliflower' (Daudt *et al*. 2018). Lesions caused by papillomaviruses mostly occur in the head, cervix, dorsal areas, abdomen, teat, areola, and mucosa of the genital and intestinal canals of cattle (Roperto *et al*. 2015). BPV of different genera may result different types of lesions in various parts of the body. Clinical findings supported by immunohistological studies are important tothe diagnosis of BPV. Besides clinical diagnosis, laboratory techniques such as Southern blotting, dot blotting, enzyme-linked immunosorbent assays (ELISA), and polymerase chain reaction (PCR) tests are also used (Araldi *et al*. 2017, Ugochukwu *et al*. 2019).

To protect animals from papillomas, many treatment methods were have been tried, such as including surgical intervention, electrocautery, ligature applications, cryotherapy, autohemotherapy, immunomodulation and homoeopathic medicine. In addition, applications of macrolides, such as azithromycin and chemicals such as vincristine, and lithium antimony thiomalate have been used (Maclachlan *et al*. 2011, Araldi *et al*. 2017, Daudt *et al*. 2018; Ugocjukwu *et al*. 2019). Different types of vaccines have also been administered as treatment (Hamad *et al*. 2012, Kale *et al*. 2019).

Levamisole (an anthelmintic) is commonly used in the treatment of parasitic infections in cattle and is a strong immune modulator. It can strengthen the cellular immunity of immune-suppressed animals and is effective in the treatment of tumours, inflammation, and chronic diseases (Kaya 2000). The *Tarantula cubensis* extract may play a role in treatment and has an immune stimulant effect on metabolism (Özyurtlu and Aslan 2007). This extract has been used for treating canine teat tumours, cattle podiatry, foot-and-mouth disease, ecthyma (orf virus), abscesses, and ulcers (Gültiken and Vural 2007, Paksoy *et al*. 2015). Ivermectin is commonly used to treat parasitic cattle infections and has antitumour effects (Drinyaev *et al*. 2004).

In this study, we were determined the efficacy of ivermectin, levamisole, *Tarantula cubensis* extract, autovaccine, and a combined levamisole and *Tarantula cubensis* extract combination in the treatment of cutaneous BPV infections detected by virological and clinical examinations in 12-36-month-old cattle.

Materials and methods

Ethics Approval

This study was conducted after the approval of the Burdur Mehmet Akif Ersoy University Animal Testing Local Ethics Council (MAKÜ-HADYEK-18.03.2020 and No: 630).

Study Animals

This study conducted between March 2020 and August 2020, used 12-36-month-old 60 cattle of different breeds and genders that had multiple warts on various parts of their bodies. The general overview on the animals used in the study is presented in Table I. The cattle were raised on small family farms and in herds of up to 30 animals. However, the animal's care and feeding conditions were not adequate for animal welfare (insufficient rations, unsuitable barn conditions, overcrowding of animals, etc.). Cattle from large-scale commercial farms with good feeding conditions, which are more suitable for animal welfare, and previously treated for medical or surgical papillomatosis were not included in the study.

Table I. *General information about animals of used in study.*

Data of Animals	Number of Animal Sampled (*n*)
Age	
12-18 months	19
18-24 months	28
24-36 months	13
Gender	
Female (♀)	31
Male (♂)	29
Races	
Montofon (Brown Swiss)	7
Simmental	11
Holstein	42

Enzyme-Linked Immunosorbent Assay (ELISA)

To detect the bovine papillomavirus antigen, blood samples were collected from the jugular veins of animals and kept in coagulant tubes (Plastic vacuum empty blood collection tube, Hema&Tube, Ankara, Türkiye). The Qualitative Bovine Papillomavirus (BPV) ELISA Kit (MyBioSource Inc., Cat. No: MBS109004; San Diego, USA) was used for diagnosis. ELISA was performed as specified by the commercial kit. The optical density of the solutions in all the wells was detected at 450 nm using an ELISA reader (Mindray MR-96A; Hamburg, Germany) with a filter. Suggested approach of the ELISA kit was performed to measure the absorbance values.

The applied treatment methods

Cattle with papillomatosis were divided randomly into six groups (n = 60), which included the control group (n = 10), animals receiving ivermectin (n = 10), animals receiving *T. cubensis* extract (n = 10), animals receiving autovaccine (n = 10), animals receiving levamisole (n = 10), and animals receiving a combination of levamisole + *T. cubensis* extract (n = 10).

The drugs administered to the groups, the doses and routes of administration are shown in Table II.

All groups were monitored for three months at 15-day intervals (Fig. 1, Fig. 2).

Table II. *Drugs administered to groups, doses and routes of administration.*

Groups	Treatment	Route of administration	Doses of administration
Group I (n=10)	No treatment (Control)	-	-
Group II (n=10)	Ivermectin	SC	Three doses of 0.2 mg/kg at weekly intervals
Group III (n=10)	*T.cubensis* extract	SC	Twice doses of 10 ml at weekly intervals
Group IV (n=10)	Autovaccine	SC	Three doses of 6 ml at 10 days intervals
Group V (n=10)	Levamisole	IM	Twice doses of 5 mg/kg at weekly interevals
Group VI (n=10)	Levamisole + *T.cubensis* extract	IM/SC	Twice doses of 5 mg/kg at weekly interevals/ Twice doses of 10 ml at weekly intervals

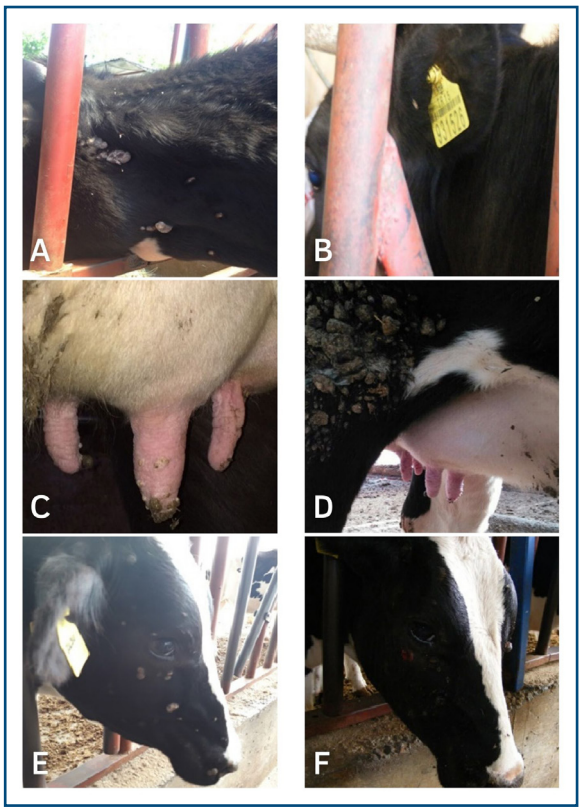

Figure 1. *Figure 1.* ***A)*** *The pretreatment with autovaccine in Group.* ***B)*** *Post-treatment with autovaccine in Group.* ***C)*** *The pretreatment with* T. cubensis *extract in Group* ***D)*** *Post-treatment with T. cubensis extract in Group.* ***E)*** *The pretreatment Levamisole in Group.* ***F)*** *post-treatment with Levamisole in Group. (Results).*

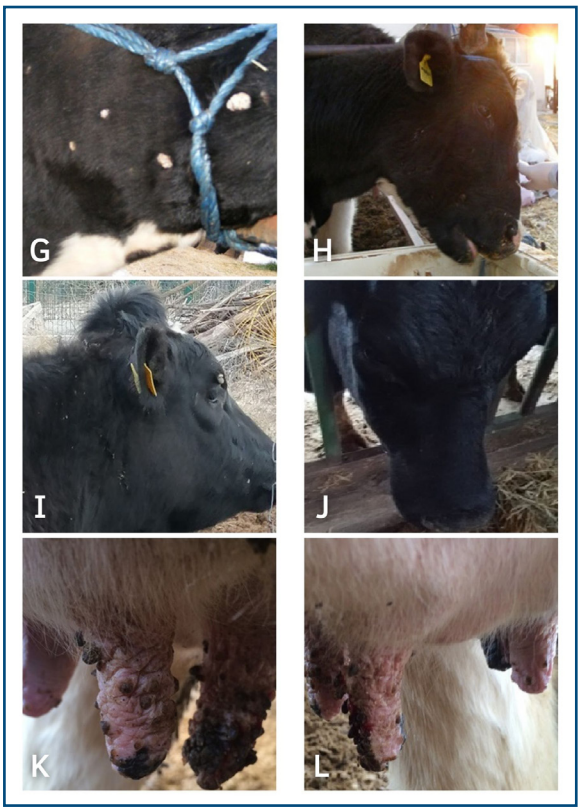

Figure 2. ***G)*** *The pretreatment with Ivermectin in Group.* ***H)*** *Post-treatment with Ivermectin in Group.* ***I)*** *The pretreatment with Levamisole* + T. cubensis *extract combination in Group.* ***J)*** *Post-treatment with Levamisole* + T. cubensis *extract combination in Group.* ***K-L)*** *No recovery was observed in the Control Group during the study period. (Results).*

Autovaccine

The autovaccine was prepared following Hunt's protocol (Hunt 1984). Papillomas weighing 4–5 g, collected from the animals, were brought to the laboratory under a cold chain. The samples were mixed with 1/10 phosphate-buffered saline (PBS) and crushed using sterile sand. This mixture was thereafter emptied through a filter into a clean beaker. The filtrate was transferred to a sterile glass tube and centrifuged for 30 min at 4 °C and 3,000 rpm. The supernatant obtained after centrifugation (10 ml) was transferred to another tube, and 0.04 ml of 40% formaldehyde was added to it. This was

incubated for 24 h on a stove at 37 °C with the inlet kept open. After incubation, the fluid was drained. into a vial with a dark hue through injector filters with a 0.22 µm pore size. The antibiotics (1%) produced by combining crystal penicillin (200.000 IU/10 mL) and streptomycin (250 mg/10 mL) were added to this fluid and kept at 4 °C overnight. To control the sterility of the fluid, MacConkey agar planting and Sabarous agar planting were performed. The planted MacConkey agar was incubated for 48 h at 37 °C, and the Sabarous agar was incubated for five days at 37 °C. After incubation, the vaccines without bacterial or fungal contamination were used.

Statistical Analysis

The Chi-squared tests were performed to evaluate recovery between groups (Minitab 16).

Results

Enzyme-Linked Immunosorbent Assay (ELISA)

The BPV antigen was detected in all blood samples taken from the tested animals.

Clinical Examination

The distribution and localization of papillomas on the animals varied and were generally detected on the head, cervix, and teat areas. Lesions were also found in the interscapular, genital, abdominal, and thoracic areas.

Clinical Findings

Clinical controls were observed every 15 days following the treatment. In the ivermectin group, papillomas completely disappeared in two animals (20%) within 45 days, in three animals (30%) in 60 days, in one animal (10%) in 75 days, and one animal (10%) in 90 days (Fig. 2 G and H).

One animal in the *T. cubensis* extract group (10%) recovered in 45 days, two animals (20%) recovered in 60 days, two animals (20%) recovered in 75 days, and one animal (10%) recovered in 90 days (Fig. 1 C and D). One animal in the autovaccine group (10%) recovered in 30 days, four animals (40%) recovered in 45 days, and five animals (50%) recovered in 60 days (Fig. 1 A and B).

Two animals in the levamisole group (20%) recovered in 45 days, one animal (10%) recovered in 60 days, and two animals (20%) recovered in 75 days (Fig. 1 E and F).

Three animals in the levamisole + *T. cubensis* extract combination group (30%) recovered in 45 days, five animals (50%) recovered in 60 days, and one animal (10%) recovered in 75 days (Fig. 2 I and J).

During this period, the papillomas of the animals in the control group showed no regression (Fig. 2 K and L) (Table III).

Table III. *Recovery state of papillomas of animals in control and treatment groups.*

Groups	Working Schedule (Days)							Total* (n)	Total (%)
	0	15	30	45	60	75	90		
I[1] (n=10)	-	-	-	-	-	-	-	0	0
II[a] (n=10)	-	-	-	2	3	1	1	7[1]	70
III[b] (n=10)	-	-	-	1	2	2	1	6[1,c]	60
IV[c] (n=10)	-	-	1	4	5	-	-	10[1,b,d]	100
V[d] (n=10)	-	-	-	2	1	2	-	5[1,c,e]	50
VI[e] (n=10)	-	-	-	3	5	1	-	9[1,d]	90

* Statistical evaluation was made between lines. Row values with same superscript letters are significantly different at $p<0.05$

Statistical Results

While the highest rate of recovery was found in the autovaccine group (100%), recovery was not observed in the control group. Statistically significant differences in the recovery rates were found between the autologous vaccine group, the *T. cubensis* extract group, and the levamisole group, and between the levamisole group and the combined group. No significant differences were found between the ivermectin group and any treatment group. The

statistically significant differences between the treatment groups and the control group are shown in Table III.

Discussion

Bovine papillomavirus (BPV) is a virus that infects almost all domestic and wild ruminants worldwide forming mucosal and cutaneous warts in animals (Araldi *et al*. 2017). Thus, papillomaviruses seriously affect animals. Dairy and breeding farms have a significant influence on the global food economy. Viruses cause contagious benign or malignant lesions in the cattle on these farms, leading to enormous economic losses (Daudt *et al*. 2018). Although animals of all ages can be infected, young cattle under two years are the most commonly affected (Jelinek and Tachezy 2005). The rate of incidence of infection in the dairy herd is higher than that in the breeding herd (Araldi *et al*. 2017). BPV-borne teat papillomatosis in dairy cows is among the most important factors of economic loss (Zhu *et al*. 2019). It is impossible to milk infected animals and this hampers the production (Borzacchiello and Roperto 2008). Papillomas prevent calves from sucking as well. When pedunculated lesions on the teats of infected animals rupture, they make the area vulnerable to secondary infections, leading to secondary teat diseases such as mastitis (Campo 2002, Zhu *et al*. 2019).

Stimulating the immune system is highly crucial when treating papillomas. Cellular immunity plays a more prominent role than humoral immunity (Nicholls and Stanley 2000). Ivermectin stimulates cellular and humoral immunity, according to previous studies (Rao *et al*. 1987, Uhlir 1991).

Börkü and colleagues (Börkü *et al*. 2007) studied the effect of ivermectin in cattle with cutaneous papillomatosis. They achieved a recovery rate of 88.8% with a single dose of ivermectin injection and 77.7% with a double dose of ivermectin injection. Kırmızıgül and colleagues (Kırmızıgül *et al*. 2010) achieved a recovery rate of 87.5% with a single dose of ivermectin injection. Babu and colleagues (Babu *et al*. 2020) achieved a recovery rate of 50% with two doses of ivermectin. Moreover, Jana and Mukherjee (Jana and Mukherjee 2013) achieved 100% treatment success with the same dose of ivermectin administered three times. In this study, we achieved 70% success using double-dose ivermectin; thus, the success of our treatment was lower than that of Kırmızıgül and colleagues (Kırmızıgül *et al*. 2010) and Jana and Mukherjee (Jana and Mukherjee 2013) but similar to that of Börkü and colleagues (Börkü *et al*. 2007) and higher than that of Babu and colleagues (Babu *et al*. 2020). We concluded that these differences in the treatments' success rates depend on the administration of different doses of ivermectin, its immunostimulant efficiency in the animals and the prognosis of papillomatosis. Furthermore, the efficacy of ivermectin on papillomatosis appeared between 45th and 90th days in our study. These results were similar to those of other studies (Börkü *et al*. 2007, Babu *et al*. 2020).

In a study by Çam and colleagues (Çam *et al*. 2007), cattle papillomatosis was treated with *T. cubensis* extract, and the medicine (7.5 mL/day) was administered to the subjects subcutaneously for five days.

After the treatment, 70% of the animals recovered. Similarly, in a study by Paksoy and colleagues (Paksoy *et al*. 2015), *T. cubensis* extract was administered subcutaneously twice to the subjects with teat papilloma at weekly intervals and controls; a recovery rate of 100% was found. Babu and colleagues (Babu *et al*. 2020) reported that regression of papillomas occurred within two weeks after the injection of *T. cubensis* extract, and treatment was provided for six months. In this study, the injection of the extract of *T. cubensis* cured bovine papillomatosis in 60% of the cases between 45–90 days. Our results were similar to those obtained by Çam and colleagues (Çam *et al*. 2007), but we achieved a lower success rate than that achieved by Paksoy and colleagues (Paksoy *et al*. 2015).

Although the working mechanism of *Tarantula cubensis* extract is not completely known, it is hypothesized to stimulate the defence mechanism and form a spontaneous remission. In studies on the treatment of cutaneous papillomatosis using the *T. cubensis* extract, the recovery time and rates of cases differed considerably (Çam *et al*. 2007, Paksoy *et al*. 2015, Babu *et al*. 2020). One of the most significant factors associated with these changes is immunity levels of animals individually. Different rates of immunostimulation in animals with different immune levels might reduce the effect of *T. cubensis* extract on the treatment of cutaneous papillomatosis.

Bovine papillomatosis treatment also includes the administration of levamisole. Çam and colleagues (Çam *et al*. 2007) administered levamisole subcutaneously (2.5 mg/kg/day) for two days, followed by a gap of five days, and this procedure was continued for five weeks. After three months of treatment, the animals showed 90% recovery. In a study by Paksoy and colleagues (Paksoy *et al*. 2015) eight animals with teat papillomas were injected with 5 mg/kg intramuscular (IM) levamisole HCL two times at weekly intervals, and the recovery rate was found to be 50%.

In our study, subjects treated with levamisole showed a 50% recovery. The recovery rate was similar to that achieved by Paksoy and colleagues (Paksoy *et al*. 2015) but was lower than that achieved by Çam and colleagues (Çam *et al*. 2007) For the treatment

of cattle papillomatosis with levamisole, the chance of success increases with repetitive and prolonged administration. The duration of treatment was similar to that followed by Çam and colleagues (Çam *et al*. 2007) (45–75 days).

In our study, the animals treated with levamisole + *T. cubensis* extract showed 90% recovery. No evidence was found in the literature on the combined effect of levamisole, and *T. cubensis* extract in the treatment of BPV infection. This study was the first to investigate the combined effect of levamisole + *T. cubensis* extract on bovine papillomatosis.

The administration of an autologous vaccine is effective for treating papillomatosis. Development of neutralized antibodies against the virus by papillomavirus vaccinations, stimulation of cellular immunity, destruction of infected cells to produce early proteins, and the introduction of the virus to keratinocytes are the basic targets (Nicholls and Stanley 2000, Campo 2006). Infected animals acquire immunity against viruses related to BPV. Hamad and colleagues (Hamad *et al*. 2012) performed autologous vaccination of BPV-infected animals.

The researchers found that with the administration of the autologous vaccine, all animals recovered within 30–60 days of treatment. Biricik and colleagues (Biricik *et al*. 2003) injected 10 mL of SC autologous vaccine and found that lesions fully regressed within 45–60 days. In our study, 100% of the animals recovered fully between 30 and 60 days after administering autovaccine.

The duration and the rate of success of the treatment were similar to those of other studies (Biricik *et al*. 2003, Hamad *et al*. 2012). We demonstrated that the difference between the group in which autologous vaccine was administered and the groups in which other treatments were administered was statistically significant ($P<0.05$). We inferred that autologous vaccination is the most effective method for treating papillomatosis.

In this study, we used various immunostimulators and autologous vaccines for the treatment of cutaneous papillomatosis. We found that all applications showed significant differences in the treatment of papillomatosis, albeit to different degrees. However, in the groups in which immunostimulators were administered, lesion regressions started from day 45 and continued through day 90.

These long recovery periods might reduce production (inability to milk or suckle the calf in cases of udder papillomatosis, difficulty in feeding in cases of oral papillomatosis, etc.) and cause economic losses for the breeder. If the conditions (type of lesions, location of lesions, the prognosis of infection etc.), in such cases are favourable, however, operative interventions might yield results faster than medical treatments.

Conclusions

To summarize, when treating BPV-borne cutaneous papilloma, which is impossible to remove by surgery, the administration of ivermectin, levamisole, *T. cubensis* extract, a combination of levamisole and *T. cubensis* extract, and an autologous vaccine offered effective results. Of the three treatments, the lowest treatment efficiency was found for levamisole (50%), while the highest efficiency was for the autologous vaccine (100%). If the autologous vaccine is unavailable, a combination of *T. cubensis* extract and levamisole might be administered.

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