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# EFFECTIVENESS OF DIFFERENT TREATMENT PROTOCOLS AGAINST CUTANEOUS BOVINE PAPILLOMATOSIS (WART): A CLINICAL TRIAL STUDY

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**ABSTRACT:** Cutaneous papillomatosis in bovine is a persistent problem in Bhutan imposing heavy economic losses to the farmers and compromising animal welfare. Although there are numerous therapies with varying protocols, it is not known which therapy is the most effective. A research trial was conducted to identify the most effective treatment protocol for cutaneous papillomatosis in Bhutan. A total of 20 cases identified based on clinical manifestation were stratified into different groups based on location and morphology of papilloma. A total of 5 cases were randomly selected from the different stratified groups and assigned to each treatment arm. Four treatment options - Autovaccines, Autohaemotherapy, Ivermectin injection, and Lithium antimony were used for the study. The response to treatment was measured every 15 days for 3 months and considered successful treatment upon complete disappearance of all papillomas. Proportion of animals recovered in each treatment was calculated and compared between other groups using Chi-Square test. The overall recovery rate of 40% (95% CI 19.1-63.9%) within 90 days post-treatment was recorded in the current study. A statistically significant difference (*p=0.040*) in recovery rate among the different treatment groups was observed. Lithium group had the highest recovery rate of 80% (95%CI 28.4-99.5%) while autovaccine group had none recovered. The remission rate in the Autohaemotherapy and Ivermectin group was 60% (95%CI 14.7-94.7%) and 20% (95%CI 0.5-71.6%), respectively. All the animals with warts in udder and teat region in Lithium group (4 out of 5 animals) recovered. Comparatively, the Lithium group also had the fastest recovery rate. This study further validated the effectives of lithium against the treatment of wart in udder/treat region. Therefore, the lithium treatment protocol can be adopted for treating udder/teat warts in the country. Further studies with larger sample sizes are recommended to establish effectiveness of other treatment protocols.

**Keywords:** Autohaemotherapy; autovaccine; cutaneous; ivermectin; lithium antimony; papilloma; remission.

## 1. INTRODUCTION

Bovine cutaneous Papillomatosis or wart is a contagious disease of cattle and occurs in all age groups. It is manifested in the form of warts on the skin. It is caused by a group of DNA viruses of the subfamily Firstpapillomavirinae of Papillomaviridae family. Twelve different strains of bovine papillomavirus (BPV) have been identified (Hatama 2012). BPV-1 and BPV-2 are associated with fibropapillomas in cattle and shows an affinity for epithelial and dermal tissue (Pangty et al. 2010). The incidence is reported to be much higher in crossbred and younger animals (Eisa et al. 2000). Cattle are the main source of infection; however, halters, ropes and instruments can also serve as a

potential and indirect source of infection. Other factors that play a significant role in the occurrence of disease are malnutrition, hormonal imbalance and immunodeficiency (Araibi et al. 2004).

Cutaneous papillomatosis is transmitted through abraded skins and takes 1-12 months to manifest as papilloma (Tan et al. 2012). It usually appears as multiple, sessile, or pedunculated, circumscribed grey-white to dark brown-black outgrowth, which may be smooth surfaced, spherical, or horny. The size of warts may vary from pea-sized to a tennis ball and cauliflower-like growth. It appears on the skin over different body parts, but neck, eyelids, teats and lower line of the abdomen are the most common sites. The impact of the disease is numerous. Besides interfering with feeding, breathing and eyesight of the animals depending on the location of lesions, the infection also results in economic loss. Therefore, warts are an important clinical entity and need veterinary aids for clinical cure.

Although the papilloma usually regresses spontaneously without significant scarring, they occasionally can persist and progress to squamous cell carcinoma, hence intervention is indispensable (Campo 1997). Successful treatment of cutaneous papillomatosis has been a great challenge because effective medicines are not available. Several treatment options like antimony preparations (Jana and Mukherjee 2013; Tailor et al. 2017; Satheesha et al. 2018), homeopathic drugs (Tailor et al. 2017; Paksoy et al. 2015), autohaemotherapy (Chand et al. 2018; Biricik et al. 2003), autogenous vaccines (Vadalia et al. 2013; Ranjan et al. 2013; Turk et al. 2005) and immunomodulators like Ivermectin (Börkü et al. 2007; Puvarajan et al. 2016; Debasis and Samir Kr 2013) and Levamisole (Paksoy et al. 2015; CÌ'am et al. 2007; Pattar and Priyanka 2013) have been tried with varying degree of success.

Cutaneous papillomatosis in bovine is a persistent problem in Bhutan imposing heavy economic losses to the farmers and compromising animal welfare. In the west-central region there are numerous reports of bovine cutaneous papillomatosis cases. Autogenous vaccines and autohaemotherapy have been tried and the results were inconsistent. Successful treatment of the cases is a major challenge for the field veterinarians. Although there are numerous therapies with varying protocols, it is not known which therapy is the most effective. It is imperative to have a pragmatic and the most effective therapeutic measure in place. Therefore, this trial was planned to select the most effective therapy among various measures available.

## 2. MATERIALS AND METHODS

### 2.1 Study area

Of the five Dzongkhags (district) in the west-central region, Wangdue Dzongkhag reports the highest burden of wart cases (VIS 2018). Further, under Wangdue Dzongkhag - Gasetshogom, Gasetshowom, Phangyuel, Bjena and Rubisa gewogs (sub-district) report the highest burden. Therefore, based on the prevalence of cases and logistic convenience, these four gewogs were selected for the trial. However, during the cases selection as per the set eligibility criteria, only cases from Gasetshogom, Gasetshowom and Phangyuel Gewogs were selected (Figure 1).

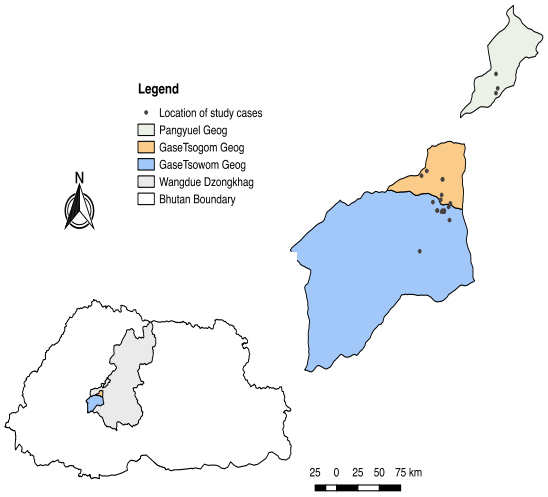


**Figure 1:** Study area

### 2.2 Selection of cases and group assignment

An inventory of bovine wart cases from the selected gewogs of Wangdue Dzongkhag was collected. A total of 32 cases were recorded from the inventory. Based on the inventory received, a team from the Regional Livestock Development Centre (RLDC), Wangdue visited the households with the reported bovine wart cases for selection.

In this study, the diagnosis of bovine papillomatosis was made based on the clinical manifestation since the structure of the papilloma on the skin can be easily observed and identified. Therefore, all the animals that have a lesion of papilloma on their skin were

considered a papilloma case and included in the study irrespective of age, sex and severity of the case. The cases that were previously treated for cutaneous papilloma and those that were in the recovery phase were not included in the trial. During the case enrollment visit, 11 cases were excluded from the trial due to non-fulfillment of inclusion criteria. As a result, a total of 20 cases were enrolled for the trial.

The selected cases were stratified into different groups based on location and morphology of papilloma. A total of 5 cases were randomly selected from the different stratified groups and assigned to each treatment arm. During the selection of cases, the owners of the animals were sensitized on purpose of the study and obtained a written consent to participate in the study.

### 2.3. Data Collection

A questionnaire was used to collect the data. Information on animals such as age, sex, breed, source of animals, and the size, number, location and morphology of the papilloma, and duration of the illness (brief history) were collected. Photographs of lesions were also taken before the start of treatment and after the completion of trial to evaluate the efficacy of the treatment given. Further, the information on the demography of herd and management were also collected.

### 2.4 Treatment protocol

Four treatment options are designed for the study that included the use of Autovaccines, Autohaemotherapy, Ivermectin injection, and Lithium antimony. Based on earlier studies, only the most effective therapy protocol of each treatment option was adapted.

#### 2.4.1 Autovaccine Therapy

The regression of wart is mediated by cellular immunity and the autogenous vaccines stimulate the immune system against the papillomaviruses. Since reports of bovine papillomatosis treatment with vaccine produced from a formalized suspension of wart tissue indicate variable result, the study adopted vaccine production protocol using 70% alcohol (Figure 2). The same protocol was used in one of the studies that resulted 100% success rate (Vadalia et al. 2013).

The cases in this group were treated with autogenous vaccine made from the warty tissue of affected animals administered in doses of 20 ml subcutaneously as a one-time single dose.

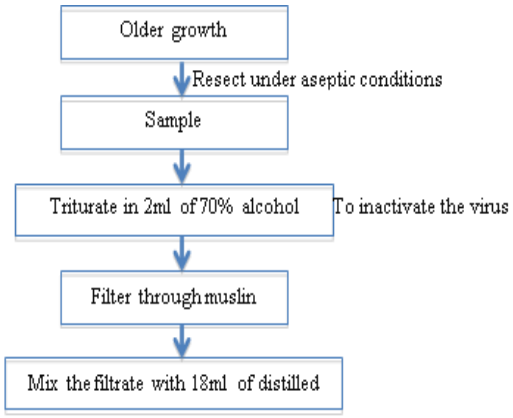


**Figure 2:** Protocol for preparation of Autovaccine

#### 2.4.2 Autohaemotherapy

Autohaemotherapy is another treatment regime for treating wart cases. It stimulates the reticuloendothelial system and increases the population of macrophage in circulating blood, which might be responsible for enhancing the regression rate of papilloma. It may help the immune system of the animal to know and identify the abnormality of the virus-induced cells and also help to correct the actual reason of failure in the immunological protective mechanism of the body, which allowed such abnormal cell proliferation. For the animals in this group, 10 ml of blood was collected from the jugular vein of each animal and injected deep intramuscularly in the same animal at a weekly interval for four weeks.

#### 2.4.3 Ivermectin

Ivermectin has an immune-modulatory and antitumor effect. Studies have shown that the use of some drugs causing non-specific immune stimulation has been found promising in clinical recovery or regression of warts. Therefore, the animals in this group were treated with ivermectin injection administered by a subcutaneous route at the dose rate of 1ml/50kg bodyweight (0.2mg/kg) on 3 occasions at 15 days interval. This protocol was adopted from a study (Puvarajan et al. 2016) where the recovery rate recorded was 95%.

#### 2.4.4 Lithium antimony

Lithium antimony has an antitumor effect. Animals in this group were treated @10-15ml deep intramuscular, depending on

the body weight of the animals. Five injections on alternative days (1, 3, 5, 7 and 9$^{th}$ day) and injection chlorpheniramine maleate @10 ml on 1, 3, 5, 7 and 9$^{th}$ day were given for each case.

### 2.5 Safety reporting

The adverse reaction of the intervention was monitored from the time of the first administration of intervention till the end of the trial i.e., day 90 post-treatment. The respective Gewog Livestock In-charges were asked to closely observe the animals for any adverse reaction for a day after every intervention administered and report to the RLDC if any.

### 2.6 Efficacy indicator

The start of treatment day was considered as 0 day and the observations regarding the response to treatment was made every 15 days for three months through field visits, using the criteria of diminishing size, shrinkage, dryness, and falling off of the papillomas. The disappearance of all papillomas was considered as complete remission. No samples were collected to evaluate the outcome measures. Further, the cases were followed up for at least 3 months post-trial for recurrence if any.

### 2.6 Data analysis

The data were managed in Microsoft excel for Mac 2011 version 14.7.7. All analyses were conducted in STATA 14 (STATA Corporation, College Station, TX). Descriptive analysis was conducted to see the difference in the characteristics of the cases in different treatment groups using Chi-Square test. The proportion of recovered animals in each treatment group was calculated. In order to see which treatment is the most effective against the bovine cutaneous papilloma, the proportion of recovered animals in each group were compared using Chi Square test. All the test with *p* value of less than 0.05 was considered statistically significant.

## 3. RESULTS AND DISCUSSIONS

A total of 20 animals affected with cutaneous papilloma were included in the present study of which only one animal is a male. The mean average age of the cases included is 5.25 years (SD± 2.07) and the age ranges from 1 to 11 years. Out of 20 animals, 75 % were jersey cross-bred and rest were local breeds. The clinical examination of animals revealed that the maximum numbers of warts were on teat/udder (65%) followed by neck region (10%), neck and eye (5%), neck and udder (5%), ear and neck (5%), Ear and udder (5%), and eye and udder (5%). Further, 80% of cases have warts on the teat/udder. At the time of examination, all the animals had multiple papilloma and size varying from a size of a peanut to an orange. However, the size of the warts observed over teats and udder were small. The papilloma grossly appeared in form of sessile and pedunculated, low flat, nodular and filiform, and smooth and horny. Detail clinical examination and gross morphological studies of the included cases also revealed that warts were sessile in 90% of the cases while it is pedunculated in 10 %. Further, most of the cases have nodular warts while an equal number of the cases have both rough and smooth surface warts. Bovine wart is a contagious viral disease of cattle caused by Bovine Papillomavirus (BPV). There are 12 well-characterised types of BPV. The co-infection by multiple BPV is also common which is responsible for variation in morphology of the papillomas developing in the affected animals (Freitas et al. 2011). In the present study, size, shape and colour of papillomas were variable, suggesting the involvement of several types of BPVs.

All the animals were apparently healthy at the time of enrolment. The distributions of the variables including the details of warts in the animals among the different treatment groups are shown in the Table 1. The table shows that there is no difference in the variables among the different treatment group including the types and location of warts.

The overall recovery rate of 40% (95% CI 19.1 - 63.9%) within the 90 days post-treatment was recorded in the current study. The lithium group had the highest recovery rate of 80% (95%CI 28.4 - 99.5%) while none of the cases in the autovaccine group recovered.

The remission rate in the Autohaemotherapy and Ivermectin group was 60% (95% CI 14.7-94.7%) and 20% (95% CI 0.5-71.6%) respectively. There is a statistically significant difference in the recovery rate of wart among the different treatment groups ($p$= 0.040). The recovery rate at different observation time (days) in the animals of different treatment groups are shown in the Table 2.

**Table 1:** Distribution of the demographic of cases (n=5) including types of warts among the different treatment groups

| Variables | Mean [SD], range, N (%) | | | | p |
|---|---|---|---|---|---|
| | Autovaccine | Ivermectin | Autohemotherapy | Lithium antimony | |
| Geogs | | | | | |
| Gasetshogom | 2 (40%) | 1 (20%) | 2 (40%) | 2 (40%) | 0.854 |
| Gasetshowom | 2 (40%) | 4 (80%) | 2 (40%) | 2 (40%) | |
| Phangyuel | 1 (20%) | 0 (0%) | 1 (20%) | 1 (20%) | |
| Gender | | | | | |
| Male | 1 (20%) | 0 (0%) | 0 (0%) | 0 (0%) | 0.368 |
| Female | 4 (80%) | 5 (100%) | 5 (100%) | 5 (100%) | |
| Breed | | | | | |
| Local | 2 (40%) | 0 (0%) | 2 (40%) | 1 (20%) | 0.402 |
| Jersey Cross | 3 (60%) | 5 (100%) | 3 (60%) | 4 (80%) | |
| Age (years) | 6 [3.24], 2-11 | 5.8 [1.30], 4-7 | 4.6 [1.14], 3-6 | 4.6 [1-7] | 0.444 |
| Body condition Score | | | | | |
| 3 | 2 (40%) | 0 (0%) | 1 (20%) | 0 (0%) | 0.059 |
| 4 | 2 (40%) | 1 (20%) | 4 (80%) | 4 (80%) | |
| 5 | 1 (20%) | 4 (80%) | 0 (0%) | 1 (20%) | |
| Types of warts | | | | | |
| Sessile | 4 (80%) | 5 (100%) | 5 (100%) | 4 (80%) | 0.528 |
| Pedunculated | 1 (20%) | 0 (0%) | 0 (0%) | 1 (20%) | |
| Morphology of wart | | | | | |
| Low flat | 0 (0%) | 0 (0%) | 1(20%) | 0 (0%) | 0.651 |
| Nodular | 1 (20%) | 3 (60%) | 1(20%) | 4 (80%) | |
| Filiform | 2 (40%) | 1(20%) | 1(20%) | 1(20%) | |
| Low flat & Nodular | 1 (20%) | 0 (0%) | 1 (20%) | 0 (0%) | |
| Nodular & filiform | 1 (20%) | 1 (20%) | 1 (20%) | 0 (0%) | |
| Surface of wart | | | | | |
| Smooth | 1 (20%) | 4 (80%) | 1 (20%) | 3 (60%) | 0.264 |
| Horny | 3 (60%) | 1 (20%) | 2 (40%) | 2 (40%) | |
| Both | 1 (20%) | 0 (0%) | 2 (40%) | 0 (0%) | |
| Location of wart | | | | | |
| Udder/teat | 3 (60%) | 4 (80%) | 2 (40%) | 4 (80%) | 0.697 |
| Other part of body | 1 (20%) | 0 (0%) | 2 (40%) | 1 (20%) | |
| Both | 1 (20%) | 1 (20%) | 1 (20%) | 0 (0%) | |
| Size of wart | | | | | |
| Large | 3 (60%) | 0 (0%) | 1 (20%) | 1 (20%) | 0.167 |
| Small | 2 (40%) | 5 (100%) | 4 (80%) | 4 (80%) | |

In the Lithium group, four out of five animals recovered. All the recovered animals had warts on teats/udder region. The only animal in the group, which did not respond to the treatment, had warts on the neck region. Almost complete recovery or complete shedding of warts irrespective of size, shape and morphology in this mode of treatment was recorded as early as 15 days post-treatment (DPT) (n=1). Regression of warts (diminution in size, drying, fissure formation and desiccation) in the remaining animals started at 15 DPT (n=3), sloughing or shedding of warts was recorded at 30 DPT (n=3) and at 45 DPT, rest of the animals (three out of four) completely cured. In the animal in which complete regression was not recorded at 90 DPT, the lesions started to shrink at 30 DPT and fall at 45 DPT. However, no complete recovery was recorded even at 90 DPT.

The second highest recovery rate was

**Table 2:** Detail of complete regression of warts in different treatment groups

| Treatment Group | No. of case recovered at 15-day interval post treatment | | | | | | Total no of recovered cases | Proportion of cases recovered (95% CI) | *p* |
|---|---|---|---|---|---|---|---|---|---|
| | 15 | 30 | 45 | 60 | 75 | 90 | | | |
| Autovaccine | - | - | - | - | - | - | 0 | 0 % | 0.040 |
| Autohaemotherapy | - | 1 | - | - | 1 | 1 | 3 | 60% (14.7-94.7 %) | |
| Ivermectin | - | 1 | - | - | - | - | 1 | 20 % (0.5-71.6%) | |
| Lithium | 1 | - | 3 | - | - | - | 4 | 80% (28.4-99.5%) | |

noticed in Autohaemotherapy. Three animals from a total of five animals recovered. However, the time taken for the recovery was quite long when compared to the lithium group. The changes in the lesion started only at 30 DPT with complete recovery of one animal at 30 during the same time. The rest of the animals (n=2) had complete recovery only at 75 DPT and 90 DPT. Although the changes in lesion like desiccation and shrinkage in the size was noticed at 45 DPT, there was no sign of falling off of warts even at 90 DPT. The location of warts has no difference in the effectiveness of treatment in this group. Animals with the wart on teat as well as on the other part of the body have recovered. Similarly, the unrecovered group has animals with wart both on the teat and other body parts.

In the other two treatment groups, the outcome of the treatment was poor. Only one animal in the ivermectin group and not a single recovery was recorded in the autovaccine group. The recovered animal in the ivermectin group has warts on teats. Although there were changes noticed in the lesions, only one animal recovered after observing them for 90 DPT. Apart from desiccation of filiform warts in a few animals, not many changes were noticed in the autovaccine group. In fact, there was a progressive growth of warts in some animals. In all the groups, no recurrence of wart was observed during the three months observatory period in clinically cured animals.

Among the different treatment groups in the current study, the highest success rate of 80% (four animals out of five animals recovered) was recorded in the lithium group. Interestingly, all the recovered animals in this group were those animals, which have warts on the teats/udder region. Further, the morphology of warts in these animals was found to be smaller sized with a narrow base. The only one which did not respond to treatment, had warts on the neck region and the size is also larger with wide base compared to the ones which had warts on teats. The current study findings are in line with what Jane and Mukherjee (Jana and Mukherjee 2013) have reported. They have used the same treatment protocol and achieved a success rate of 70%. Further, they had also reported that antimony preparation works well in bovine cutaneous wart where the lesions are small, nodular or filiform and cauliflower-like and it has the least or poor efficacy on treating large fibropapilloma bearing wide base and big sized flat warts. The non-responsiveness of warts located in other regions to lithium treatment is also reported in one study (Chand et al. 2018), which was later recovered by Autohaemotherapy. There are also studies where lithium was found to be effective against the treatment of wart in other location as well. However, their treatment protocol consists of a combination of lithium and some other medicines like ranitidine (Dileepkumar and Ansari 2012) and Thuja (Tailor et al. 2017). This study findings suggest that lithium is also effective against warts in other regions when given in combination with other therapies. The rate of regression in this treatment group was also fast when compared to other groups. Warts in four animals located in the teat region resolved within six weeks DPT. Similar responsiveness was also recorded in one of the studies (Jana and Mukherjee 2013), wherein the lesions started to fall off within four weeks of post-treatment. Therefore, the study conclude that Lithium antimony preparation is the most effective against the smaller warts on the teat region compared to other treatment protocols.

Warts are usually seen in immuno-compromised animal. Autohaemotherapy stim ulates reticuloendothelial system and increases the population of macrophage thereby up-scaling the immunity of the animals (Turk et al. 2005). In the present study, 60% of the animals (3 animals) in the group recovered at 90 DPT. While comparing the recovery rate by the location of warts, it is more in animals with warts located in other regions (n=2) then in teats (n=1). This finding of more effectiveness of autohaemotherapy against the wart in other body parts when compared to teat warts is consistent with the findings of the previous study (Ranjan et al. 2013; Chand et al. 2018), which also used the same treatment protocol.

In the current study, response to ivermectin was not satisfactory. Only one animal (20%) recovered from a total of five animals, which is contradictory to the findings of other studies (Börkü et al. 2007; Puvarajan et al. 2016; Debasis and Samir Kr 2013) wherein the response rate was quite overwhelming. The treatment protocols used in this study were similar to the past successful studies conducted. The only difference between the past and current study is the age of the animals included in the study. Past studies were carried out in younger animals, and this study included animals of

age ranging from 7 months to 4 years. The highest success rate was also recorded in the study where the younger animals were included. The mean age of the animals in this group was 5.8 years ranging between 4 to 7 years. The recovery of the youngest animal (4years) in this group and also the findings of previous studies (Börkü et al. 2007; Puvarajan et al. 2016; Debasis and Samir Kr 2013) suggest that ivermectin is more effective against warts in younger animals. However, further studies need to be conducted to validate the current findings.

There are different methods of preparation of autogenous vaccines and treatment protocols. Reports of bovine papillomatosis treatment with vaccine produced with formalin, normal saline and glycerin saline solution of wart tissue indicate variable results. The only study using vaccine prepared with 70% alcohol to inactivate the virus resulted in 100% success (Vadalia et al. 2013). However, none of the animals in the group recovered in this study with the same protocol. Therefore, it is inconclusive to state that vaccine produced with alcohol is always effective. Results of the past studies and acknowledging that the autogenous vaccine stimulates the immune system, leaves room for further studies under Bhutanese condition.

## 4. CONCLUSION

This study has further validated the effectiveness of lithium against the cutaneous bovine papillomatosis. Therefore, lithium can be used for treating the wart on the teat and udder region. The study also suggests that autohaemotherapy is more effective against the warts located in other body parts when compared to warts in udder/teat region. The use of other treatments such as Autovaccines and Ivermectin injection needs to be further validated by conducting more similar studies.

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