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Immunological effects of self-blood vaccination and autogenous vaccination in cattle infected with the cutaneous papillomatosis virus

Efectos inmunológicos de la autohemovacunación y la vacunación autógena en bovinos infectados con el virus de la papilomatosis cutánea

Efeitos imunológicos da auto-hemovacinação e da vacinação autógena em bovinos infectados pelo vírus da papilomatose cutânea

Andrés Suárez-Usbeck[1*]; Pamela Vinueza[2,3]; Marilyn Mora[2]; Anahí Carrasco[1]; Tirsa Echeverría[1]; Andrea Vela[4]

[1]*Grupo de Investigación Ecuatoriano en Medicina y Sanidad Animal (GIEMSA, IIEMSA), Ecuador.*
[2]*Facultad de Ciencias Pecuarias, ESPOCH, Ecuador.*
[3]*Grupo de Investigación en Ciencias Veterinarias (GICV), ESPOCH, Ecuador.*
[4]*Universidad Técnica de Ambato, UTA, Ecuador.*

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***Corresponding author:** Calle el Batán, Edificio Estrella X, Quito, Ecuador. Email: mvzandressuarez@gmail.com

Abstract

Background: Bovine papillomatosis represents a condition with significant economic implications in dairy farming. Papillomavirus induces benign tumors that can progress to cancer. Autogenous vaccination (*ATV*) and self-blood vaccination (*AHV*) are particularly interesting therapeutic strategies for treating cutaneous papilloma resulting from bovine papillomavirus (*BPV*). **Objective:** To investigate the immunological effects of *AHV* and *ATV* in cattle in Ecuador. **Methods:** One hundred fifty animals with clinical symptoms of *BPV* were diagnosed using PCR and distributed among different groups. To create the vaccines, a total of 50 animals were used in the *AHV* protocol (n = 25) with 20 mL and (n = 25) with 10 mL blood doses administered to them. In the *ATV* protocol another 50 animals were used, (n = 25) animals with 10 mL and (n = 25) with 20 mL. The vaccines were stored at 4°C until use. Vaccines (*AHV* and *ATV*) were administered subcutaneously four times at one-week intervals at 20 and 10-mL dosages, respectively. Hematological and immunological analyses involved the collection of blood samples both before and after each vaccination. The remaining subjects (n = 50) functioned as the positive control group (C). **Results:** A significant increase was observed in leukocyte count (14.5; 14; 15.4; 16 x 10^3/mm^3), lymphocyte percentage (55; 52; 58; 62%), and interleukin-6 levels (0.85; 0.80; 0.95; 0.97 ng/L) in both *ATV* at 10 and 20 mL doses and *AHV* at 10 and 20 mL doses compared to the positive control (C) group (Leu: 13 x 10^3/mm^3; Lym: 50%; *IL-6*: 0.54 ng/L). Notably, neutrophil (33; 35; 44; 40%) and monocyte (5; 8; 12; 13%) percentages also increased in *AHV* and *ATV*. Within the first month post-vaccination, both *AHV* and *ATV* exhibited signs of regression in cutaneous papilloma. **Conclusion:** This study underscores autogenous vaccination as a practical therapeutic approach, demonstrating its effectiveness in inducing lesion regression in cattle infected with papillomavirus.

This effect occurs especially by stimulating the production of *IL-6* and lymphocytes.

Keywords: *autogenous; autovaccine; self-blood vaccine; bovine papillomavirus; cattle; IL-6; immunology; leukocyte; papillomavirus; PCR; virus; vaccine.*

Resumen

Antecedentes: La papilomatosis bovina representa una condición de considerable importancia económica en la ganadería lechera. El papillomavirus induce tumores benignos que pueden progresar hasta cáncer. Entre los diversos enfoques terapéuticos existentes para tratar la papilomatosis cutánea resultante del virus de la papilomatosis bovina (*VPB*) se destacan la autohemovacuna (*AHV*) y la vacuna autógena (*ATV*). **Objetivo:** Examinar los efectos inmunológicos de *AHV* y *ATV* en el ganado bovino en Ecuador. **Métodos:** Se diagnosticaron 150 bovinos con síntomas de papilomatosis cutánea mediante PCR y se distribuyeron en diferentes grupos. Para crear las vacunas, se utilizaron un total de 50 animales en el protocolo *AHV*, n = 25 con dosis de 20 mL y n = 25 con dosis de 10 mL de sangre. En el protocolo *ATV*, se utilizaron otros 50 animales (n = 25 con 10 mL y n = 25 con 20 mL). Las vacunas se almacenaron a 4°C hasta su uso. Las vacunas (*AHV* y *ATV*) se administraron subcutáneamente cuatro veces con intervalos de una semana en dosis de 20 y 10 mL, respectivamente. Se realizaron análisis hematológicos e inmunológicos de muestras de sangre antes y después de cada vacunación. **Resultados:** Tanto en *ATV* (10 y 20 mL) como en *AHV* (10 y 20 mL) se observó un aumento de leucocitos (14.5; 14; 15.4; 16 x 10^3/mm^3), linfocitos (55; 52; 58; 62%), interleucina-6 (0.85; 0.80; 0.95; 0.97 ng/L), neutrófilos (33; 35; 44; 40%) y monocitos (5; 8; 12; 13%) en comparación con C+ (Leu: 13 x 10^3/mm^3; Lym: 50%; *IL-6*: 0.54 ng/L; Neu: 34%; Mon: 6.5%). Durante el primer mes después de la vacunación se observaron signos clínicos de regresión del papiloma cutáneo. **Conclusiones:** La vacunación autógena es una intervención terapéutica práctica y efectiva que promueve eficazmente la regresión de lesiones en bovinos infectados con papilomavirus. Este efecto se da especialmente mediante estimulación de la producción de IL-6 y linfocitos.

Palabras clave: *autógeno; autovacuna; autohemovacuna; inmunológia; ganado; IL-6; leucocito; papilomavirus; PCR; vacuna; virus; virus del papiloma bovino.*

Resumo

Antecedentes: A papilomatose bovina representa uma condição de considerável importância econômica na pecuária leiteira. O papilomavírus é conhecido por induzir o desenvolvimento de tumores benignos nos hospedeiros, que podem progredir para cânceres malignos. Existem diversas abordagens terapêuticas para tratar a papilomatose cutânea resultante do vírus da papilomatose bovina (*BPV*), e a auto-hemovacina (*AHV*) e a vacina autógena (*ATV*) destacam-se entre elas. **Objetivo:** Examinar os efeitos imunológicos da *AHV* e da *ATV* em bovinos no Equador. **Métodos:** Foram diagnosticados 150 bovinos com sintomas de papilomatose cutânea por PCR e distribuídos em diferentes grupos. Para criar as vacinas, um total de 50 animais foi utilizado no protocolo *AHV*, sendo n=25 com doses de 20 mL e n=25 com doses de 10 mL de sangue. No protocolo *ATV*, foram utilizados outros 50 animais, sendo n=25 com 10 mL e n=25 com 20 mL. As vacinas foram armazenadas a 4°C até o uso. As vacinas (*AHV* e *ATV*) foram administradas quatro vezes de forma subcutânea, com intervalos de uma semana, em doses de 20 e 10 mL, respectivamente, para cada grupo de tratamento. Foram realizadas análises hematológicas e imunológicas, com coleta de amostras de sangue antes e depois de cada vacinação. **Resultados:** Os resultados demonstraram, nos grupos *ATV* (10 e 20 mL) e *AHV* (10 e 20 mL), um aumento notável no número de leucócitos (14,5; 14; 15,4; 16 × 10^3/mm^3), linfócitos (55; 52; 58; 62%), interleucina-6 (0,85; 0,80; 0,95; 0,97 ng/L), neutrófilos (33; 35; 44; 40%) e monócitos (5; 8; 12; 13%) em comparação com o grupo controle positivo (C+) (Leu: 13 × 10^3/mm^3; Lym: 50%; *IL-6*: 0,54 ng/L; Neu: 34%; Mon: 6,5%). Nas vacinas *AHV* e *ATV* no primeiro mês após a vacinação, observaram-se sintomas clínicos de regressão dos papilomas cutâneos. **Conclusão:** O estudo destaca a vacinação autógena como uma intervenção terapêutica prática e eficaz, que promove efetivamente a regressão das lesões, especialmente mediante a estimulação da produção de *IL-6* e linfócitos em bovinos infectados com papilomavírus.

Palavras-chave: *autógeno; auto-hemovacina; autovacina; imunologia; gado; IL-6; leucócito; papilomavírus; papilomavírus bovino; PCR; vacina; virus.*

Introduction

Papillomaviruses (PVs) are DNA viruses that specifically infect epithelial cells and are characterized by the absence of an envelope (Aksoy *et al.*, 2017). The PV family comprises five genera that affect cattle, namely *Deltapapillomavirus, Xipapillomavirus, Epsilonpapillomavirus, Dyoxipapillomavirus*, and *Dyokappapapillomavirus*. To date, 27 bovine papillomavirus (*BPV*) types have been identified, with four of them present in Ecuador: *BPV-1, BPV-2, BPV-6, and BPV-10* (Daudt *et al.*, 2018; Méndez *et al.*, 2021). It has been observed that lesions caused by *BPV* Types 1, 2, 13, and 14 (*Deltapapillomavirus*) pose a higher risk (Daudt *et al.*, 2018).

The prevalence of *BPV* infections is global. Cutaneous papillomas manifest as typically benign tumors characterized by a complicated etiology and pathogenesis, marked by epithelial proliferation. The various transmission pathways of *BPV* (direct and indirect contact) significantly contribute to the transmission of cutaneous papillomatosis, incorporating a myriad of risk factors (Atasever *et al.*, 2005; Dagalp *et al.*, 2017; Daudt *et al.*, 2018; Saied *et al.*, 2021). *Papillomavirus* infections, particularly, tend to spread among animals with compromised immune systems (Alcigir *et al.*, 2016; Alcigir and Timurkan, 2018). Various treatment approaches for *BPV* infection encompass antimony preparations, homeopathic drugs, ivermectin, and autogenous vaccination (Ranjan *et al.*, 2013; Saied, 2021).

The objective of this study was to examine the immunological effects of self-blood vaccination (*AHV*) and autogenous vaccination (*ATV*) in cattle infected with *BPV* in Ecuador.

Materials and Methods

All experiments were carried out in strict accordance with the principles of animal welfare and were approved by the Committee of Ethics in Animal Experimentation of the GIEMSA Welfare Department (protocol No. PI01/2023).

The experimental design involved 150 cattle exhibiting symptoms of cutaneous papilloma disease, diagnosed through Polymerase Chain Reaction (*PCR*) analysis as described by Méndez *et al.*(2021). To extract DNA from the collected samples, 25 mg of tissue was processed using the DNeasy Blood & Tissue kit (Qiagen, Valencia, California, USA) following the manufacturer's protocol. The extracted DNA was stored at -80°C until use.

The DNA samples were subjected to *PCR* using the primer pairs FAP-59/FAP-64 (Macrogen, Seoul, Republic of Korea) (FAP-59: 5'-TAACWGTIGGICAYCCWTATT-3'; FAP-64: 5'-CCWATATCWVHCATITCICCATC-3') and MY-09/MY-11 (IDT, San Diego, California, USA) (MY-09: 5'-CGTCCAAAAGGAAACTGAGC-3'; MY-11: 5'-GCACAGGGACATAACAATGG-3'). The primer pairs were designed to target the open reading frame of the major capsid protein *L1* gene, which is highly conserved across all types of bovine and human papillomaviruses.

This protocol was based on the study by Aydin *et al.*(2020) and Doğan *et al.*(2021). For *AHV*, a total of 50 cattle were utilized. Among them, n = 25 animals received 20-mL blood doses, while another n = 25 received 10-mL blood doses. Simultaneously, in *ATV*, another set of 50 cattle was included. Among these, n = 25 cattle were administered 20-mL doses, and the remaining n = 25 received 10-mL doses of autogenous vaccines. The control group (C) consisted of n = 50 animals diagnosed positive for *BPV* but untreated.

The *AHV* protocol involved collecting 10-mL and 20-mL blood samples from each animal, treating them with 0.5% formalin to inactivate any present pathogens and maintain the stability of the suspension (Fernandes *et al.*, 2022). The preparation of *ATV* vaccines involved 5 g of papilloma tumor collected from the animals, which was transported to the laboratory under a cold chain. The samples were prepared following the protocol of Yildirim *et al.*(2023). The vaccines were then stored at 4°C until use.

The administration of vaccines (*AHV* and *ATV*) was performed subcutaneously, with four doses given at one-week intervals. Two dosages were employed, 20 mL and 10 mL, representing the treatment groups.

Hematological and immunological analyses were carried out through the collection of 20-mL blood samples. Parameters examined included total leukocyte count, lymphocyte count, interleukin-6 concentration, neutrophil count, and monocyte count. The data were presented as mean values ± standard error. Statistical comparisons were made between the treatment groups and the C group.

We recorded leukocytes, lymphocytes, interleukin-6, neutrophils, and monocytes counts in both *AHV* and *ATV* groups compared to the C group. Additionally, clinical observations of lesion regression in cutaneous papilloma post-vaccination were recorded in all groups.

Statistical analysis

All statistical analyses were conducted using SPSS v. 26. Categorical variables were examined through cross-tabulation, and percentages were compared using Pearson's χ^2 test. Quantitative variables were presented as mean ± standard error (SE). ANOVA was used to compare the Control and Treatment groups, considering fixed effects. Additionally, a non-parametric test (Mann–Whitney U test) was employed for comparing the Control and Treatment groups. Differences were deemed significant at $p < 0.05$.

Results

Figure 1 illustrates a portion of the *PCR* results, where analyses were conducted on 150 bovines distributed into one control group and four treatment groups (*AHV* T1, n=25; *AHV* T2, n=25; *ATV* T1, n=25; and *ATV* T2, n=25, respectively).

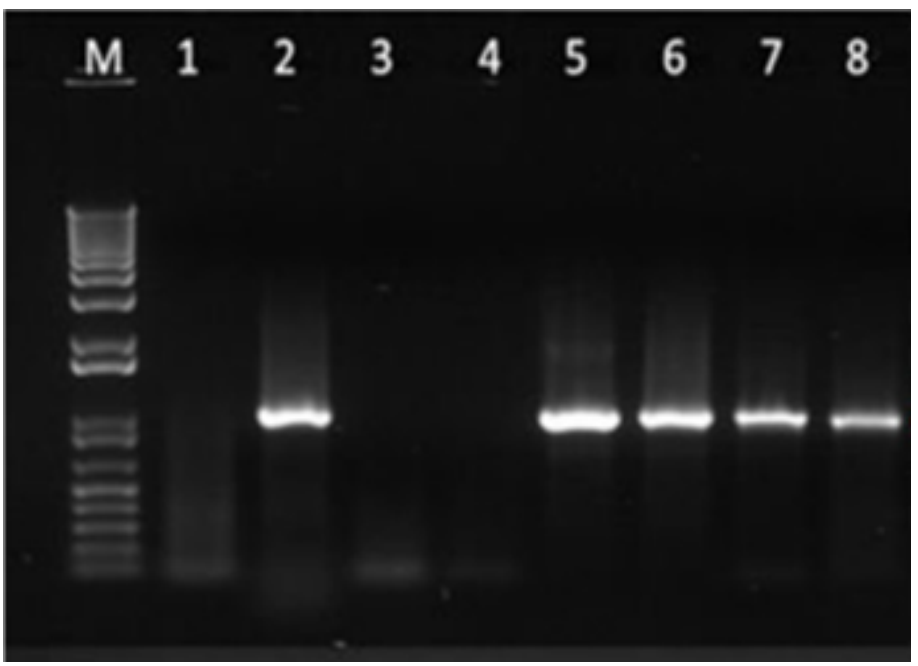

Figure 1. Electrophoresis results on a 1% agarose gel showing detection of *BPV* by *PCR*. Lane M: Molecular weight marker (1 kb Plus DNA Ladder). Lane 1: Negative control. Lane 2: Positive control. Lanes 3–8 correspond to *BPV* samples.

Table 1 shows the hematological and immunological parameters analyzed, including leukocyte count, lymphocyte count, interleukin-6 concentration, neutrophil count, and monocyte count.

Table 1. Hematological and immunological parameters of *ATV* and *AHV* vaccines.

Variable	C	AHV T1 (10mL)	AHV T2 (20 mL)	ATV T1 (10 mL)	ATV T2 (20 mL)	p-value
	n=50	n=25	n=25	n=25	n=25	
Leukocyte (10^3/mL)	13	14.5*	14*	15.4*	16*	0.04
Lymphocyte (%)	50	55	52	58	62	0.08
interleukin-6 (ng/L)	0.54	0.85*	0.80*	0.95*	0.97*	0.02
Neutrophil (%)	34	33	35	44	40	0.15
Monocyte (%)	6.5	8*	8*	12*	13*	0.03

* Significant difference ($p < 0.05$).

The analysis of the results reveals statistically significant differences in several measured variables between the control (C) group and the treatment groups (*AHV* T1, *AHV* T2, *ATV* T1, *ATV* T2). Specifically, the leukocyte count (p=0.04), monocyte count (p=0.03), and interleukin-6 concentration (p=0.02) show statistically significant differences. These findings suggest that the administration of treatments affected the immune responses and interleukin-6 concentration compared to the control group.

On the other hand, although the differences in lymphocyte (%) and neutrophil (%) counts did not achieve statistical significance at 0.05 level (p=0.08 and p=0.15, respectively), they may still indicate trends that could be relevant in a clinical context. These results emphasize the importance of considering multiple variables and their interactions when assessing the impact of various treatments on the immune system.

Discussion

Papillomavirus, a viral pathogen notorious for triggering benign tumors in mammals, has garnered extensive attention due to its implications for animal health and the livestock economy (Ugochukwu *et al.*, 2019). Notably, *BPV*-induced cutaneous papillomatosis has driven investigations into effective therapeutic strategies, with a focus on *AHV* and *ATV* as promising approaches for managing the infection (Skeate *et al.*, 2016). This study contributes to the understanding of the immunological effects of *AHV* and *ATV* in cattle, particularly within the context of Ecuadorian livestock, where dairy production holds significant importance.

The relevance of this study aligns with previous research emphasizing the efficacy of autogenous vaccines in controlling bovine papillomatosis (Skeate *et al.*, 2016). The study by Tozato *et al.*(2013) underscores the economic relevance of bovine papillomatosis in dairy production, emphasizing the urgency of developing therapies that not only alleviate symptoms but also promote the regression of cutaneous lesions.

Our findings, demonstrating significant increases in leukocytes, lymphocytes, interleukin-6, neutrophils, and monocytes in both the *AHV* and *ATV* groups (P<0.05) compared to the control group (C), provide novel insights into the immunological responses induced by these vaccines (Fernandes *et al.*, 2022; Khattab *et al.*, 2023). Consistent with existing literature, *ATV* was found to increase leukocyte counts, particularly lymphocyte counts and ratios. We observed that *ATV* promoted tumor tissue

regression by elevating the levels of lymphocytes, which are pivotal for cellular immunity, and neutrophils, which are responsible for phagocytic activity (Aydin *et al.*, 2020).

The experimental design, involving 150 cattle diagnosed with cutaneous papilloma through Polymerase Chain Reaction (*PCR*) analysis, adhered to ethical standards for animal welfare. Our study employed two dosages, 20 mL and 10 mL, for *AHV* and *ATV*, demonstrating lesion regression within the first month post-vaccination (Lacey *et al.*, 1999; Pathania *et al.*, 2011; Salib and Farghali, 2011). These results are consistent with prior investigations on the implications of bovine papillomatosis disease and underline the importance of refining immunotherapeutic strategies for managing papillomavirus infections in cattle (Dal Pozzo and Thiry, 2014; Knight, 2015; Marć *et al.*, 2015). Overall, our study contributes valuable data to the field, enhancing our understanding of the immunological effects of *AHV* and *ATV* in the context of bovine papillomatosis.

In conclusion, this study investigated the immunological effects of *AHV* and *ATV* in cattle infected with *BPV* within the Ecuadorian livestock industry. The investigation, grounded in the implications of papillomavirus in the dairy sector, addressed the pressing need for effective therapeutic interventions against bovine papillomatosis. Building upon previous studies on autogenous vaccines, this study demonstrated that *AHV* and *ATV* induced statistically significant increases in immune system activity. The results contribute novel insights into the immunological responses induced by *AHV* and *ATV*, providing valuable data for the refinement of therapeutic interventions against bovine papillomatosis and reinforcing the importance of considering multiple variables in assessing the impact of treatments on the immune system.

Declarations

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Conflicts of interest

The authors declare they have no conflicts of interest regarding the work presented in this report.

Author contributions

Conceptualization, A.S.-U.; methodology, A.S.-U.; software, M.T.T.; validation, V.P., V.A. C.A. and M.T.T.; formal analysis, M.T.T..; investigation, A.S.-U; resources, A.S.-U; data curation, A.S.-U. and M.T.T.; writing original draft preparation, A.S.-U., V.P., V.A. C.A. and M.T.T; project administration, A.S.-U.

Use of artificial intelligence (AI)

No AI or AI-assisted technologies were used during the preparation of this work.

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