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Influence of vaccination time relative to heifers' synchronization on infectious bovine rhinotracheitis virus antibody and stress markers responses

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ABSTRACT

Objective: To characterize the influence of infectious bovine rhinotracheitis (IBR) vaccination time regarding the start of estrus synchronization on antibody titer, inflammatory reaction and oxidative stress in Holstein heifers.

Methods: Twenty-four heifers (12.5 to 14.0 months old) were allocated into two experiments with 12 heifers in each, according to history of bovine herpesvirus (BoHV-1) vaccination (naïve and booster vaccinated). Heifers in each experiment were assigned to Pre-synch, In-synch and control groups. Pre-synch and In-synch groups received IBR vaccine on Day -3 and Day 5 of estrus synchronization start, respectively. Control animals remained unvaccinated but synchronized. Blood samples collected on Day 0 (day of vaccination), 7, 14 and 46 and assayed for IBR antibody titer, C-reactive protein (CRP), and total antioxidant capacity (TAC).

Results: The experiments showed invariably high BoHV-1 antibody titer after vaccination with live attenuated gE deleted vaccine or polyvalent vaccines containing chemically altered BoHV-1 in all vaccinated-synchronized animals compared to the control from Day 0 to Day 46 in naïve heifers, and from Day 7 to 46 in booster vaccinated animals. In booster vaccinated animals, CRP was low in Pre-synch group on Day 7 ($P<0.05$), and both synchronized groups on Day 14 and 46. TAC levels of Pre-synch and In-synch naive heifers, and pre-synch booster heifers were lower than its control group on Day 0, and in naïve vaccinated In-synch group than booster In-synch on Day 7 ($P<0.05$).

Conclusions: The timing of estrus synchronization related to vaccination did not alter BoHV-1 antibody levels but affected CRP and TAC which make the animals liable for pathogen invasion and/or oxidative stress during the post-vaccinal period.

KEYWORDS: BoHV-1 antibody; Heifers; C-reactive protein; Oxidative stress; Synchronization; Vaccine; Total antioxidant capacity

1. Introduction

The effects of vaccination time coincident with estrus synchronization and insemination/breeding is unclear. Many animal owners try to reduce the labor and costs of vaccination as well as distress on animals brought by estrus synchronization by doing them together. Nevertheless, simultaneous vaccination is beneficial by providing fetal and maternal protection against diseases but not impede reproduction when administered to cattle earlier than estrus synchronization and breeding[1].

Estrus synchronization is one of the most important and widely applicable assisted reproductive technologies currently available in

Significance

Few studies examined the interaction of medications and viruses, but none delineated the antibody response or oxidative stress to infectious bovine rhinotracheitis vaccination around synchronization time. Although infectious bovine rhinotracheitis antibody titre was not affected by vaccination, markers of inflammation and oxidative stress were disturbed. Animal liability to infection or stress increases in vaccinated-synchronized animals, even though their immune status to certain diseases were not affected.

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animal farms[2]. Estrus synchronization and artificial insemination (AI) reduce the cost of obtaining a pregnancy, which supports the added investment in genetics[3]. Estrus synchronization effectively increases the proportion of females that become pregnant early during the breeding season, resulting in shorter breeding/calving periods and more uniform calf[2,4]. The protocols of estrus synchronization in cycling cows are generally based on either long-term progestin treatment (to inhibit LH release) or prostaglandin F2α treatment (to induce corpus luteum regression), or their combinations[5].

Several research observed the antiviral activity of prostaglandin on Parainfluenza 3 virus, Sendai virus, vesicular stomatitis virus, encephalomyocarditis virus, and herpes simplex virus I[6–10]. This inhibition occurred on several levels of viral replication which is not only as a result of direct effects on the virus, but also due to the effect on immune system response to prostaglandin[11].

The complex inter-relationship between progesterone and viral infection or immune reaction is unclear. Immune cells express progesterone and/or estrogen receptors which allow hormonal immunomodulation[12]. Progesterone-based compounds alter cellular signaling and activity that influence the outcome of infections at mucosal sites such as genital tracts[13]. Progesterone showed an enhancement of the protective immune response after immunization with *Chlamydia abortus*[14].

Bovine herpesvirus (BoHV-1), also known as infectious bovine rhinotracheitis (IBR), is an alpha herpesvirus pathogen that causes respiratory, reproductive (including abortion) and neurological diseases in cattle[15,16]. Killed- and modified-live viral vaccines of BoHV-1 are able to stimulate the immune system. Various internal and external factors negatively affect the organism's welfare status and induce energy-consuming mechanisms and predispose to subsequent illness. Therefore, vaccination timing should be optimized to maternal immune, nutrition, stress statuses which may influence vaccine efficacy[17]. Guidelines settled by vaccine manufacturers advocate avoiding vaccination of stressed cattle[18] which may experience an inhibited inflammatory response and reduced immune response[19,20].

Quantitative and qualitative monitoring of stress levels include assay of innate immune markers such as acute phase proteins, and assay of oxidative stress markers such as reactive oxygen species[21].

C-reactive protein (CRP) is an acute phase reactant that is widely used as a definitive marker for systemic inflammation[22]. It is a promising biomarker of pathogen invasion, immunological disorders, metabolic stress, and cardiovascular diseases[23]. Oxidative stress showed an impact on various pathological and immunological processes such as bacterial sepsis and parturition and lactation-induced metabolic disorders in animals[24].

Recent research focused on the development of estrus synchronization protocols that facilitate fixed-time AI (FTAI). Additionally, no published research has engaged in characterizing the immunological responses during estrus synchronization protocols in heifers. The present work aimed to analyze the antibody as well as selected stress markers in heifers that vaccinated with BoHV-1 vaccine as influenced by timing of synchronization and vaccination.

2. Materials and methods

2.1. Drugs and vaccines

Drugs were purchased from Ceva Sante Animale. Drugs include an intra-vaginal progesterone device (PRID Delta®, 1.55 g progesterone per device), gonadotrophic releasing hormone (Cystrolin®, 50 μg/mL Gonadorelin diacetate tetrahydrate), and prostaglandin F2α (Enzaprost T, 5 mg/mL dinoprost trometamol).

Vaccines were a commercially available BoHV-1 live attenuated gE deleted vaccine (Bovilis IBR Marker live, MSD animal health), a live, attenuated marker vaccine per dose containing at least 5.7 log10 TCID 50 of gE− BHV-1 strain GK/D, and polyvalent vaccine containing chemically altered BoHV-1 (Cattle Master GOLD FP 5 L5, Zoetis Inc.), a combined freeze-dried preparation of chemically altered strains of IBR and PI3 viruses, and modified live BRSV, plus a liquid adjuvanted preparation of inactivated bovine viral diarrhea virus (types 1 and 2) and inactivated cultures of the five Leptospira serovars).

2.2. Animals and experimental design

Twenty-four Holstein heifers (12.5 to 14.0 months old) which were sero-screened for BoHV-1 were enrolled into two experiments according to history of BoHV-1 vaccination. Heifers were managed according to routine animal husbandry procedures and were fed an age-appropriate grain and hay ration ad libitum during the study period. All heifers were examined with ultrasound five times before the start of the synchronization protocol for assurance of animals fertility status[25].

Twelve naïve heifers (not previously vaccinated) and other twelve booster vaccinated heifers (previously vaccinated against BoHV-1 six months before experiment) were used in the first and second experiments, respectively.

Heifers in each experiment were randomly and equally assigned to one of three treatment groups, four animals per each group, according to time of vaccination in relation to synchronization start point. Pre-synch group was given a single dose of IBR vaccine three days before synchronization. In-synch group was given a single dose of IBR vaccine five days after synchronization start. The control group was synchronized but remained unvaccinated.

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2.3. Estrus synchronization

All animals were given PGF2α three days before synchronization protocol which lasted for eight days [2,26]. Briefly, progesterone was administered per vagina and GnRH was given intramuscularly on the start day of synchronization protocol. Five days later, a single intramuscularly injection of PGF2α was given. The vaginal device was removed and PGF2α was injected intramuscularly again on the 6th Day. Finally, GnRH was given intramuscularly on the 8th Day, coincident with AI.

2.4. Vaccination

Bovilis IBR Live® (IBR live attenuated gE deleted) was injected intramuscularly, while Cattle master Gold (Polyvalent vaccine contain live chemically altered IBR) injected subcutaneously by the same person, and animals were observed daily for post-vaccinal reaction and/or clinical signs. In the first experiment, all heifers received a commercially available BoHV-1 monovalent live attenuated vaccine. Animals in the second experiment were vaccinated with polyvalent vaccine containing chemically altered BoHV-1.

2.5. Blood samples

Blood samples were collected at the day of vaccination, 7th, 14th and 46th days post vaccination. Blood samples were drawn into clot activator vacutainer tubes by jugular venipuncture. Sera were collected after centrifugation at 500 ×g for 15 min and stored at -20℃ until they were assayed for IBR virus antibody titer, CRP (marker of inflammation), and total antioxidant capacity (TAC, marker of oxidation-reduction potential).

2.6. Blood analysis

2.6.1. IBR antibody titer evaluation

Before testing for IBR virus antibody, all sera samples were heat inactivated for 30 min at 56℃ in a water bath. Serum samples were tested for BoHV-1 antibodies by ID Screen® IBR indirect ELISA kit (Ref. No. IBRS-5P, Innovative Diagnostics, France) using ELISA reader (Stat Fax 2100, Italy) at 450 nm wave length according to the manufacturer's instructions.

2.6.2. Analysis of CRP

Sera were tested for CRP through turbidimetry method using available commercial kits (CRP Turbi Latex, REF: 560 001, Spectrum For Diagnostic Industries - Free Zone, Egypt) at 540 nm wave length according to the manufacturer's instructions.

2.6.3. Analysis of TAC

TAC analysis was done colorimetrically using available commercial kits (CAT No. TA2513, Bio diagnostic for diagnostic and research reagents, Egypt) at 505 nm wave length according to the manufacturer's instructions.

2.7. Statistical analysis

Data presented as mean (± SEM) were tested for normality with Shapiro-Wilk Test. Differences between synchronized-vaccinated groups and control in each experiment were tested with One way ANOVA and post-hoc with Tukey using IBM® SPSS (Statistical Package for the Social Sciences) Ver. 23. Differences between matched groups in the two experiments were tested with unpaired t-test with Welch's correction. The magnitude of changes was evaluated with area under curve using GraphPad Prism 10 Statistics. Correlation between tested parameters was verified with Pearson correlation. The P-value was set at 0.05 for significant differences between groups.

2.8. Ethical approval

All procedures and treatments of animals were approved by the Institutional Animals Care and Use Committee, Research Ethics Board, Faculty of Veterinary Medicine, Benha University according to animal welfare guidelines (No. BUFVTM 44-06-23).

3. Results

3.1. Effect of interaction of vaccination–synchronization time on BoHV–1 antibody titers

BoHV-1 antibody titer was measured in naïve-vaccinated and booster-vaccinated synchronized nulliparous heifers (Figure 1, Supplementary Table 1). Naïve heifers (Pre-synch and In-synch groups) showed a significant increase in BoHV-1 antibody titer compared to control non-vaccinated heifers on Day 0, 7, 14 and 46 post-vaccination($P<0.05$). On the other hand, booster vaccinated heifers (Pre-synch and In-synch groups) showed a similar increase on Day 7 ($P<0.05$), Day 14 ($P<0.01$) and Day 46 ($P<0.05$). The variation between naïve and booster vaccinated animals was not evident along the experimental period, though there was a tendency for BoHV-1 antibody titer to be higher in Pre-synch booster vaccinated than that of naïve animals on Day 0, which is not statistically significant. As expected, BoHV-1 antibody in the control booster vaccinated group was higher than control naïve animals from Day 0 to Day 46 post-vaccination($P<0.05$).

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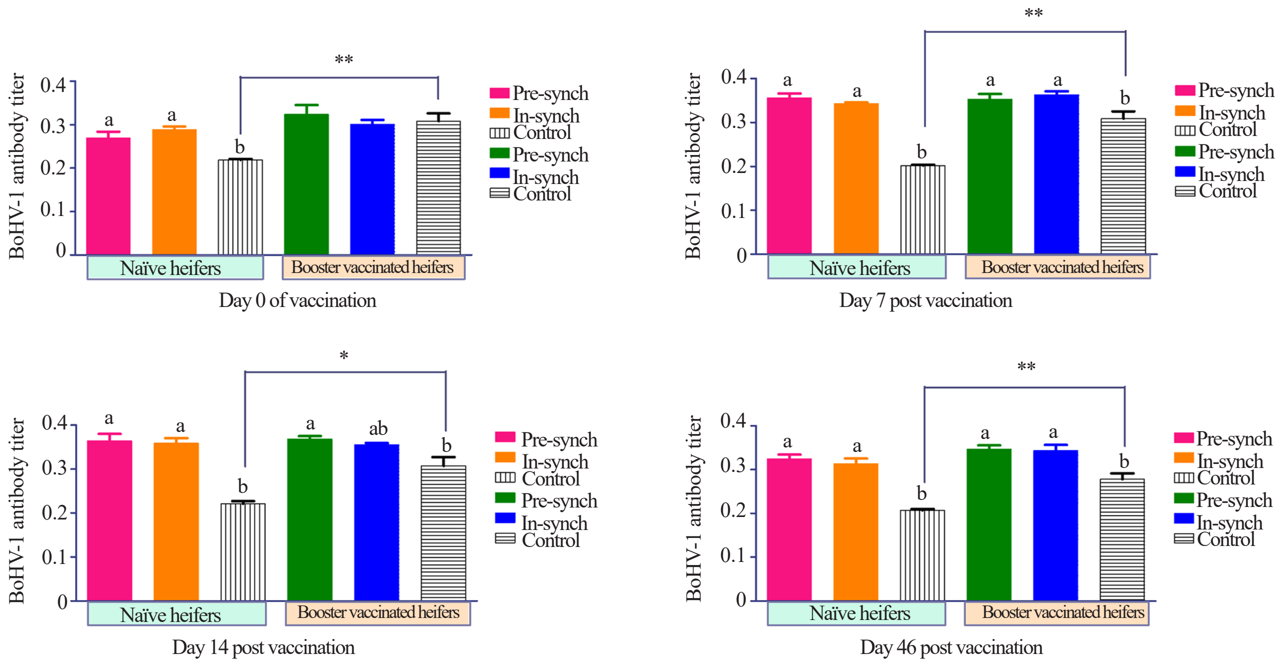

Figure 1. Effect of timing of vaccination with synchronization on IBR antibody titer in naïve (NH) and booster vaccinated (BVH) synchronized heifer. Columns with different letters were significantly different compared with its controls (P< 0.05). * and ** indicated significant differences at P< 0.05 and 0.01, respectively.

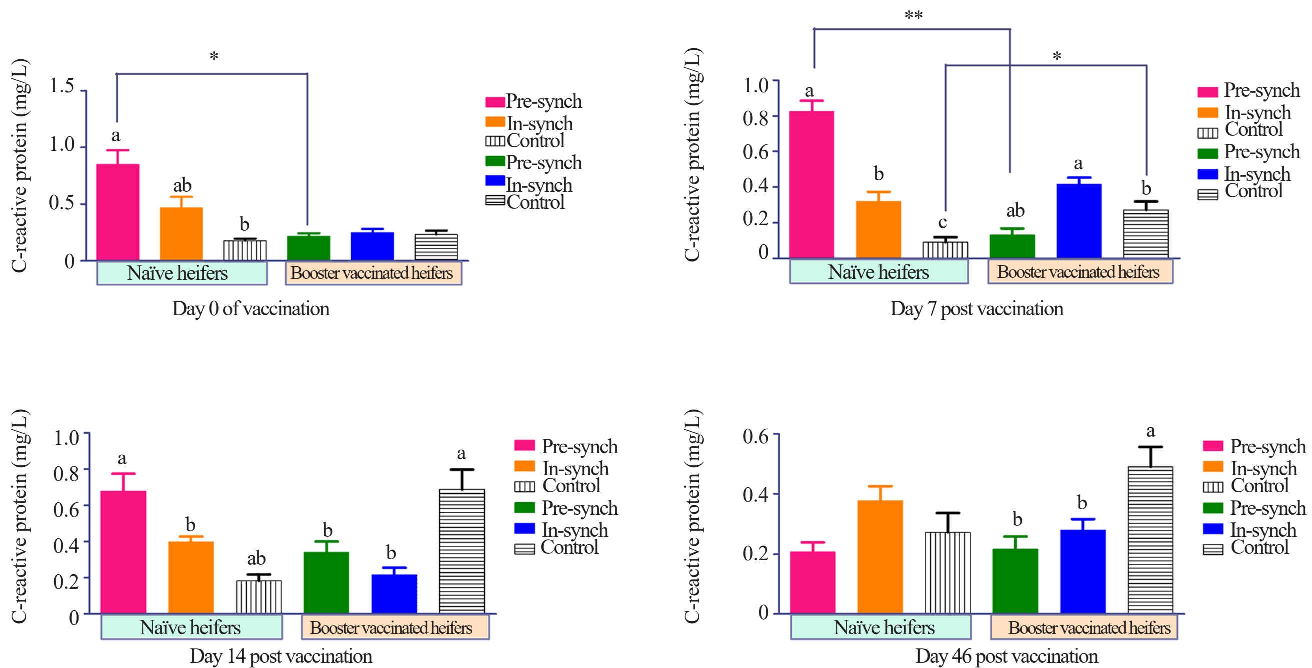

Figure 2. Effect of timing of vaccination with synchronization on C-reactive protein in naïve (NH) and booster vaccinated (BVH) synchronized heifer. Columns with different letters were significantly different compared with its controls (P< 0.05). * and ** indicated significant differences at P< 0.05 and 0.01, respectively.

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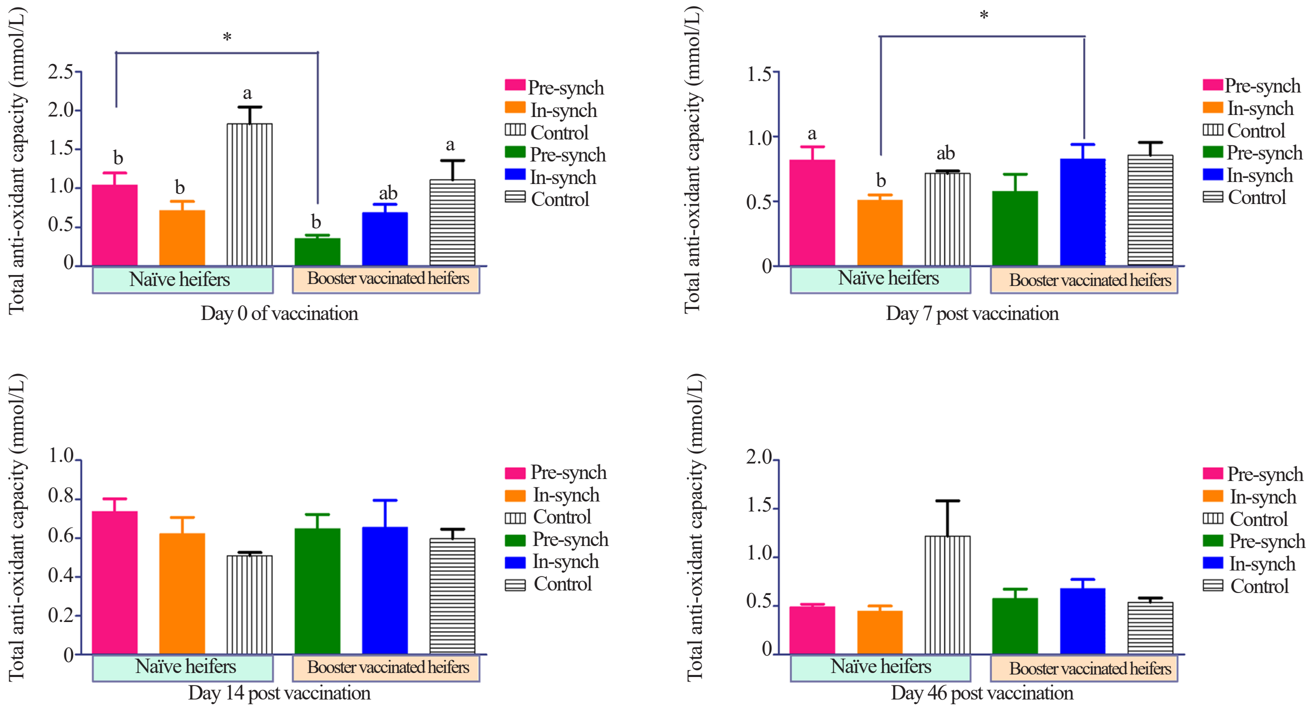

Figure 3. Effect of timing of vaccination with synchronization on Total anti-oxidant capacity in naive and booster vaccinated (BVH) synchronized heifer. Columns with different letters were significantly different compared with its controls ($P< 0.05$). * indicated significant differences at $P< 0.05$.

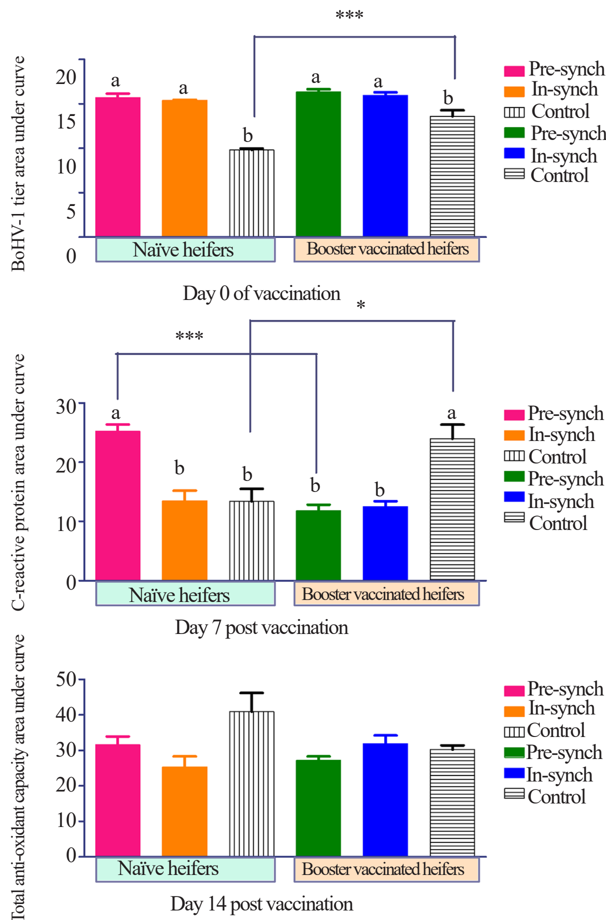

Figure 4. Change in the quantitative magnitude (represented by area under the curve) of IBR antibody, C-reactive protein, and total anti-oxidant capacity in naïve (NH) and booster vaccinated (BVH) synchronized heifers. Columns with different letters were significantly different ($P< 0.05$). * and *** indicated significant differences at $P< 0.05$ and 0.01, respectively.

3.2. Effect of interaction of vaccination–synchronization times on CRP level

CRP was measured in BoHV-1 vaccinated synchronized heifers (Figure 2, Supplementary Table 2). In naïve heifers, CRP was maximally higher in Pre-synchronized group on Day 0, 7 ($P<0.05$) and 14, while in the In-synch group increased on Day 7 ($P<0.05$), compared to control animals. In booster vaccinated heifers, CRP in the In-synch group significantly increased on Day 7 compared to the control ($P<0.05$). Interestingly, CRP was lower in booster vaccinated synchronized groups on Day 14 ($P<0.05$) and 46 compared to the control. Comparing the naïve and booster vaccinated heifers, Pre-synch group showed an elevated CRP levels on Day 0 ($P<0.05$), Day 7 ($P<0.01$) and Day 14. CRP exhibited higher levels in control booster vaccinated animals than control naïve heifers on Day 7 (P<0.05) and Day 46.

3.3. Effect of interaction of vaccination–synchronization times on TAC levels

Mean TAC was measured in naïve, and booster vaccinated synchronized heifers vaccinated with IBR polyvalent vaccine (Figure 3, Supplementary Table 3). On Day 0, synchronized naïve and booster vaccinated heifers showed lower TAC than control ones ($P<0.05$, $P=0.05$ respetively). Nevertheless, TAC was upsurged in

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Pre-synchronized naïve heifers on Day 7 compared to the In-synch group ($P<0.05$). Moreover, TAC in naïve synchronized heifers showed a tendency to decrease compared to the control animals on Day 46. Comparing naïve to booster vaccinated animals, TAC was higher in naïve Pre-synch animals on Day 0 ($P<0.05$), and in booster vaccinated In-synch animals on Day 7 ($P<0.05$) compared to Pre-synch booster and In-synch naïve groups, respectively.

3.4. Quantitative magnitude of IBR antibody, CRP and TAC capacity in synchronized animals

Quantitative magnitude (represented by area under curve) of IBR antibody, CRP, and TAC were measured in synchronized animals (Figure 4, Supplementary Table 4). As expected, the overall all antibody titer was higher in all vaccinated groups compared to the control, without significant influence of vaccination timing in relation to start of synchronization program. CRP was higher in naïve Pre-synch group than control ($P<0.01$), but it was lower ($P<0.05$) in synchronized (Pre-synch and In-synch) booster vaccinated animals than its contemporary control heifers. Nevertheless, CRP was higher in naïve Pre-synch animals than the matching group of the booster vaccinated heifers ($P<0.05$), while the overall changes in TAC tended to be lower in naïve In-synch group than the control animals. Pearson correlation analysis showed a significant negative correlation between IBR antibody titer and TAC ($P<0.01$, r=-0.329) (Figure 5). Nonetheless, there was no significant relation between IBR antibody titer and CRP or between CRP and TAC.

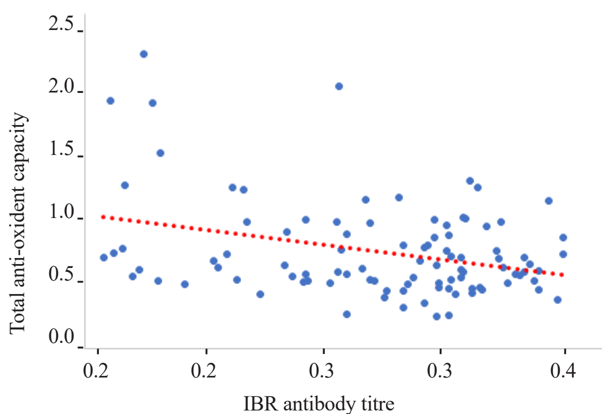

Figure 5. Correlation between IBR antibody titer and total anti-oxidant capacity in vaccinated heifers

4. Discussion

Several researchers studied the effect of vaccination on corpus luteum function[11], serum hormone concentrations and conception rates[2] and pregnancy success[27] in naïve heifers. However, there were no published papers characterized the immunological responses during estrus synchronization protocols in heifers. In the present study, vaccination with BoHV-1 vaccines invariably induced high IBR antibody titer in all synchronized animals compared to the control. In booster vaccinated groups, CRP response was attenuated in Pre-synch group on Day 7, and in both synchronized groups on Day 14 and Day 46. TAC decreased in all vaccinated animals (except booster vaccinated In-synch group) on Day 0 compared to the control, and in naïve vaccinated In-synch group than booster In-synch on Day 7.

Vaccinations with either a modified live or inactivated virus vaccines administered prior to breeding are the most effective way to control the spread of BoHV-1 and prevent its adverse effects on reproduction including abortions[17]. Modified live virus vaccines generated both humoral and cell-mediated immune responses, while inactivated vaccines elicited solely a humoral immune response that is primarily antibody specific[28,29]. In the present study, IBR antibody titer following vaccination with monovalent live attenuated gE deleted, or chemically altered live BoHV-1 vaccines was invariably high in all synchronized naïve heifers (from Day 0 to Day 46), and booster vaccinated animals (on Day 14 and 46) compared to the control, indicating that the antibody levels were not affected by the synchronization timing. The high BoHV-1 antibody level in all synchronized animals regardless vaccine type might be related to IFNγ production by Th1 helper cells and IL-4 production by Th2 helper cells that stimulated cellular and humoral responses, respectively[30]. The release of IFNγ, IL-4 and TNFα cytokines by peripheral blood mononuclear cells of vaccinated animals initiates the connection to the adaptive response, including presenting the antigen to lymphocytes[31]. There were differences in BoHV-1 antibody levels between monovalent live attenuated and chemically altered live polyvalent vaccinated groups in the present study. This could be related to its boosting effect in previously vaccinated heifers[32]. Slight differences in antibody level within vaccinated groups might be attributed to the vaccination time[32]. Despite, prostaglandins regulate a wide variety of physiological processes, including inflammation, immune responses, and cell differentiation[33], in this study, synchronization protocol with PGF2α showed no effect on the pattern of BoHV-1 antibody levels in the two experiments.

CRP and TAC are potential biomarkers of immune challenge[34] and/or host response to stress[35], respectively. In this study, analysis

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of CRP using area under the curve declared its increase in naïve Pre-synch group, but it was lower in booster synchronized groups than control. CRP was generally high in Pre-synch naïve heifers (from Day 0 to 14) than control and Pre-synch booster vaccinated group. These results signaled the role of progesterone-prostaglandin based synchronization protocol in attenuating the post-vaccinal inflammatory reaction to IBR vaccination. Progesterone hormone markedly suppressed cytotoxicity and decreased gene expression of IFNB, IL6 and IL1B after viral infection in vitro[36]. This unpleasant effect would increase susceptibility to diseases and uterine invasion with pathogens. Progesterone-treated animals (rodent model) exposed to intrauterine *Chlamydia trachomatis* infection showed increased susceptibility to infection through suppression of spleen-cell proliferation[37]. TAC is the sum of the activity of heterogeneous antioxidant compounds[38]. The decrease in oxidative stress relieving potential (marked with TAC) was recorded in the current experiments in all vaccinated animals compared to control on Day 0 and naïve vaccinated In-synch group compared to its corresponded booster group on Day 7. This indicated the lower ability of vaccinated animals to withstand oxidative stress during the post-vaccinal period. Such observation was evidenced by the significant negative correlation shown in this study between IBR antibody titer and TAC. Besides, this effect was augmented with progetsrone-prostaglandin based synchronization protocols, which probably explains why vaccine manufacturer guidelines recommend avoiding vaccination of compromised cattle[18] that may experience an inhibited inflammatory response and reduced immune response vaccination[19,20].

5. Conclusions

Although BoHV-1antibody levels were not affected by timing of estrus synchronization protocol, CRP and TAC were profoundly affected during the post-vaccinal reaction period. Therefore, it is highly recommended to avoid stressed animals undergoing vaccination and synchronization for breeding simultaneously. Further studies are required to investigate the interaction of vaccination and synchronization on the immune status in the challenge of diseases.

Conflict of interest statement

The authors claim there is no conflict of interest.

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This study receives no extramural funding.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Yousef W contributed to the conceptualization, methodology, experimental studies, data acquisition, and writing of the original draft. El Nahas EM was responsible for the design, definition of intellectual content, manuscript editing and review, as well as supervision. Abouel-Roos MEA also contributed to the design, definition of intellectual content, manuscript editing and review, and supervision. Sosa GAM was involved in validation, design, definition of intellectual content, manuscript editing and review, and supervision. Kandiel MMM contributed to the conceptualization, methodology, data analysis, experimental studies, manuscript preparation, editing, review, and supervision. The authors would like to affirm that the manuscript has been read and approved by all authors. They confirmed that the requirements for authorship, as stated earlier in this document, had been met, and each author believes that the manuscript represents honest work.

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Supplementary Table 1. BoHV-1 antibody titer in naïve and booster vaccinated animals as affected by timing of vaccination with synchronization protocol.

Animal groups	Day of vaccination (Day 0)			Day 7 post-vaccination			Day 14 post-vaccination			Day 46 post vaccination		
	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)
Pre-synch group	0.27±0.02^{a}	0.32±0.02	0.08	0.36±0.01^{a}	0.35±0.01^{ab}	0.84	0.36±0.02^{a}	0.37±0.01^{a}	0.82	0.32±0.01^{a}	0.35±0.01^{a}	0.14
In-synch group	0.29±0.01^{a}	0.30±0.01	0.37	0.34±0.00^{a}	0.36±0.01^{a}	0.11	0.36±0.01^{a}	0.36±0.00^{a}	0.77	0.31±0.01^{a}	0.34±0.01^{a}	0.16
Control	0.22±0.00^{b}	0.31±0.02**	0.01	0.20±0.00^{b}	0.31±0.02^{b**}	<0.01	0.22±0.01^{b}	0.31±0.02^{b*}	0.05	0.21±0.00^{b}	0.28±0.01^{b**}	0.01
P	<0.05	0.62		<0.05	0.05		<0.05	0.01		<0.05	<0.05	

Data (Mean ± SEM, *n*=4/group) with different letters within the same column were significantly different. * and ** signified marked difference between booster vaccinated and naïve animals (Unpaired *t*-test with Welch's correction).

Supplementary Table 2. C-reactive protein (mg/L) in naïve and booster vaccinated animals as affected by timing of vaccination with synchronization protocol.

Animal groups	Day of vaccination (Day 0)			Day 7 post-vaccination			Day 14 post-vaccination			Day 46 post vaccination		
	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)
Pre-synch group	0.85±0.13^{a*}	0.22±0.03	0.05	0.82±0.06^{a**}	0.13±0.04^{ab}	<0.05	0.68±0.10^{a}	0.34±0.06^{b}	0.06	0.21±0.03	0.22±0.04^{b}	0.86
In-synch group	0.47±0.10^{ab}	0.25±0.03	0.17	0.32±0.06^{b}	0.42±0.04^{a}	0.25	0.18±0.04^{b}	0.22±0.04^{b}	0.57	0.38±0.05	0.28±0.04^{b}	0.18
Control	0.18±0.02^{b}	0.23±0.04	0.24	0.09±0.03^{c}	0.27±0.05^{b*}	0.05	0.40±0.10^{ab}	0.69±0.11^{a}	0.11	0.27±0.06	0.49±0.07^{a}	0.06
P	<0.05	0.78		<0.05	<0.05		0.05	<0.05		0.68	0.09	

Data (Mean ± SEM; *n*=4/group) with different letters within the same column were significantly different. * and ** signified marked difference between booster vaccinated and naïve animals (Unpaired *t*-test with Welch's correction).

Supplementary Table 3. Total anti-oxidant capacity (mmol/L) in naïve and booster vaccinated animals as affected by timing of vaccination with synchronization protocol.

Animal groups	Day of vaccination (Day 0)			Day 7 post-vaccination			Day 14 post-vaccination			Day 46 post vaccination		
	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)
Pre-synch group	1.04±0.15^{b*}	0.35±0.04^{b}	0.05	0.82±0.10^{a}	0.58±0.13	0.21	0.74±0.07	0.65±0.07	0.41	0.49±0.03	0.58±0.10	0.21
In-synch group	0.71±0.12^{b}	0.69±0.11^{ab}	0.87	0.51±0.04^{b}	0.83±0.11*	<0.05	0.62±0.08	0.66±0.14	0.85	0.45±0.05	0.68±0.09	0.18
Control	1.83±0.21^{a}	1.11±0.25^{a}	0.07	0.72±0.02^{ab}	0.86±0.10	0.25	0.51±0.02	0.60±0.05	0.17	1.22±0.37	0.54±0.05	0.20
P	<0.05	0.05		0.05	0.22		0.11	0.89		0.07	0.49	

Data (Mean ± SEM, *n*=4/group) with different letters within the same column were significantly different. * and ** signified marked difference between booster vaccinated and naïve animals (Unpaired *t* test with Welch's correction).

Supplementary Table 4. Changes in the quantitative magnitude (represented by area under the curve) of IBR antibody, C-reactive protein, and total anti-oxidant capacity in synchronized animals.

Animal groups	IBR antibody titer			C-reactive protein			Total anti-oxidant capacity		
	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)	Naïve animals	Booster vaccinated animals	*P*(*t*-test)
Pre-synch	15.71±0.45^{a}	16.35±0.31^{a}	0.35	25.24±1.11^{a***}	11.78±1.07^{b}	<0.05	31.60±2.35	27.24±1.08	0.23
In-synch	15.42±0.06^{a}	15.98±0.32^{a}	0.16	13.48±1.70^{b}	12.48±0.96^{b}	0.46	25.37±2.94	31.86±2.34	0.15
Control	9.80±0.19^{b}	13.60±0.68^{b***}	<0.05	13.37±2.15^{b}	23.96±2.37^{a*}	0.05	40.88±5.27	30.17±1.26	0.18
P	<0.05	<0.05		0.01	<0.05		0.07	0.18	

Values (Mean ± SEM, *n*=4/group) with different letters within the same column were significantly different. * and *** denoted significant differences between groups with unpaired *t*-test with Welch's correction.