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Kısa Bilimsel Çalışma / Short Communication

A meta-analysis of IBR and BVD diseases in Turkey

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ABSTRACT :

Bovine Viral Diarrhoea (BVD) and Infectious Bovine Rhinotracheitis (IBR) are the most prevalent viral diseases that cause abortion in cattle. There are many studies conducted in Turkey to show the occurrence of them. This paper aims to analyse these studies systematically. For this purpose, 11 suitable studies were selected from 1995-2014 to review. It was observed from those studies that the diseases were in high prevalence in Turkey, the prevalence of BVD and IBR ranged between 14 % - 81 % and 43 % -72 % respectively, and the animals had antibodies against both factors (1.13 odds ratio). The 1.13 odds ratio shows that BVD and IBR results are close to each other, but slightly tends to BVD.
These two diseases have been eradicated in most of the developed countries but it is not notifiable in Turkey. Control schemes, therefore, should be considered by the competent authorities and universities. Awareness of these diseases should increase to prevent reproduction losses and develop livestock industry.

Türkiye'de IBR ve BVD hastalıklarının meta-analiz incelemesi

ÖZET:

Sığır Viral Diyaresi (BVD) ve Sığırların Bulaşıcı Rinotrakeitisi (IBR) sığır abortlarına neden olan hastalıklar arasında en sık görülen iki viral hastalıktır. Türkiye'de bu hastalıkların varlığını ortaya koymak amacıyla pek çok çalışma yapılmıştır. Sunulan makalede, bu çalışmaların sistematik bir analizinin yapılması amaçlanmıştır. Bu amaçla, 1995-2014 yılları arasında uygun bulunan 11 yayın analiz için seçilmiştir. Bu çalışmalarda Sığır Viral Diyaresi (BVD) ve Sığırların Bulaşıcı Rinotrakeitisi (IBR) hastalıklarının Türkiye'de yüksek yaygınlıkta olduğu, BVD ve IBR prevalans aralığının sırasıyla % 14 - % 81 ve % 43 - % 72 arasında olduğu ve bu etkenlere karşı antikorların aynı kan serumunda birlikte görülme sıklığının yüksek olduğu görülmüştür (1,13 odds değeri). Bulunan 1.13 odds değeri, BVD ve IBR sonuçlarının birbirine yakın olduğunu, ancak az miktarda BVD'ye meyilli olduğunu göstermektedir.
Birçok gelişmiş ülkede eradike edilen fakat ülkemizde ihbarı mecburi hastalıklar listesinde yer almayan bu iki etkene yönelik kontrol önlemlerinin alınması yetkili otoriteler ve üniversiteler tarafından dikkate alınmalıdır. Reprodüktif kayıpların önlenmesi ve hayvancılığın gelişmesi için bu hastalıklarla ilgili bilinç arttırılmalıdır.

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1. Introduction

Since the importance of Bovine Viral Diarrhoea-Mucosal Disease (BVD-MD) in bovine abortions was shown in the 1980s, its importance has been increasing in cattle infertility. BVD-Virus is a pestivirus of Flaviviridae family, which is related to border disease (sheep) and classical swine fever (pigs). The infection causes low conception rate, congenital anomalies, and foetal losses in the first three months and the second three months period of pregnancy. Chances of abortion varies depending on different isolates. Abortion rates can be different on the farms; however, it might increase to 40 % in the experimental studies (1, 2).

Disease-specific antigens and antibodies are used for diagnosing BVD. It is reported that the tests are very reliable. Detection of antibodies in cattle is a widely accepted method to show individual immunity and past infections (3).

The aetiological agent of Infectious Bovine Rhinotracheitis is called Bovine Herpes Virus-1, which is a member of the Herpesviridae. It is prevalent in the world, and the disease causes latent and acute respiratory infections in cattle, characterised by conjunctivitis. Besides, it causes abortion and the form of the genital disease (Infectious pustular vulvovaginitis, IPV). In addition to those, enteritis, encephalitis, mastitis, endometritis can be seen (1, 4). Abortions caused by IBR occurred without other clinical signs. Animals usually abort after the 6^{th} month of pregnancy. Most of the aborted foetuses had undergone autolysis in IBR abortions, which indicated they had been dead 48 hours to 1 week before they were expelled (5).

In accordance with the directive of the European Union (92/65/EEC, 1999), semen used in artificial insemination and embryos in embryo transfer must be free from IBR virus. This obligation motivated the EU countries to start eradication schemes against the disease. Six EU countries and some regions have been declared IBR free. The member countries, obligatory or voluntarily, conducted eradication programs against the disease including marker vaccination and test-slaughter implementations (6).

It is seen from the Ministry of Food, Agriculture and Livestock leaflets, IBR was a notifiable disease between 1998 and 2002 in Turkey, in the scope of the old Turkish veterinary legislation (no. 3285). However, it was removed from the notifiable diseases list after that year. Similarly, it was not on the list in the new law about veterinary issues, which went into effect in 2010 (no. 5996).

Vaccination can prevent the clinical symptoms, virus replication and transmission but not the disease. There are always seropositive animals in the vaccinated infected herds. The cost of the eradication schemes should be taken into consideration before combatting the disease. Unexplained cases are sporadically seen in the officially IBR free states. Due to the latent infection of the virus, some healthy carrier animals can be culled during the eradication of IBR. Freedom from the disease cannot be achieved by vaccinating all animals alone, it should be done together with other implementations such as biosecurity, education and compensation. Voluntarily supporting IBR-free herds will be pressure on farmers as well (7). The aim of this study is to systematically review of the publications on the most important virological abortive diseases (IBR and BVD) in Turkey. Even though there were plenty of studies on the occurrence of these agents in Turkey, they were limited to certain locations; for that reason, these publications gathered and analysed systematically in this study.

Systematic review and meta-analysis:

There are different ways to research the literature. In the traditional narrative reviews, authors collect studies based on personal opinions and availability of the studies. Their interpretation and conclusion of these studies is subjective. There is not a standard format or a special method for these reviews. They are informative, but can usually have selection bias (8, 9).

On the other hand, there is a comprehensive plan and search strategy in the systematic reviews as befits the name. The results are more reliable and contain minimum bias. Systematic reviews often use statistics (meta-analysis) to synthesise the data from different studies into a quantitative conclusion (9, 10).

“Meta” is originally a Greek term, which means “after” or “beyond”; so that, a meta-analysis is an “analysis of analyses”. It is defined by Huque, as a statistical procedure that integrates the results of several independent studies

(11). Meta-analysis is optional in the systematic reviews, and many of them contain meta-analysis. It is not compulsory to use meta-analysis in the reviews; therefore, it should be done by comparable, homogeneous studies that have similar results. Even though meta-analysis is particularly suitable for serial controlled experimental studies, it is used in observational studies as well. Meta-analytical studies also have been conducting in Turkish veterinary obstetrics and gynaecology studies from time to time (4, 12).

2. Material and Methods

There are several studies on IBR and BVD that investigated the same serum in the Turkish scientific literature. These studies aim to show the diseases mentioned in animals, together and they are comparable, homogeneous and show similar effects, hence it is decided to use these works in a meta-analytical study. The 11 suitable studies, which published in English and Turkish, from different parts of Turkey between 1995 and 2014 were chosen to analyse (Table 1).

According to the EPICOT format (13) which is recommended for Health research, the population of the study is cattle, the comparison group is the IBR and BVD positive cases and the outcome, in accordance with epidemiological works (having a disease or exposure to a factor), is BVD or IBR positivity in the same blood sample. Publication bias was assessed using funnel plots.

The search strategy of this study was based upon online sources. The databases that were used for search: Pubmed, Google Scholar and Web of Science. The main keywords were IBR and BVD, serology, antibody. There were no date limitations in the search strategy as of the date of the research.

The eligibility criteria:

The studies to determine the seroprevalence of BVD and IBR virus antibodies in the same blood serum were chosen for analysis; two papers which contain vaginal swap and antigen studies were excluded. Separate antibody studies of IBR and BVD in cattle among Turkey are excluded as well. The two-by-two tables of the results of the selected 11 studies were created by using the R statistical program's rmeta package, and then the odds ratios and 95 % confidence intervals of them were calculated.

Statistical analysis:

The prevalence ratio's are provided separately both IBR and BVD; however, during the analysis phase, odds ratio's of the occurrence of these diseases were used.

The effect size, the magnitude and the consistency of works are examined while assessing a meta-analytical work. A forest plot, which displays the direction of the effect, provided in a meta-analytical study, and the diamond figure in the forest plot represents the cumulative effect. The fixed effects model is selected in the studies conducted with a single population, for example, in the serial controlled experiments. In the observational studies, on the other hand, the random effects model is applied. Significant heterogeneity test results are preferable but it is not always obtained.

The heterogeneity thresholds, according to The Cochrane hand book, is 0% to 40%: might not be important; however, 30% to 60% may present moderate, 50% to 90% substantial and 75% to 100% considerable heterogeneity.

Since the studies in this project contain the disease prevalence of different regions, it is expected to have different results and high heterogeneity levels. In this analysis, the heterogeneity was shown with the fixed effect test, and then the odds ratios provided with random effect size model (14).

Compared to the Mantel–Haenszel Method, Peto Method was chosen for studies with low effect size, small odds ratio and sample sizes. The results of this study were shown in the tables both with the Mantel–Haenszel and the Peto Methods.

The Begg's test evaluate whether there is a significant correlation between the ranks of the effect estimates and the ranks of their variances, while the test of Egger take linear regression to show the relation between the standardized effect estimates and the standard error (SE). Significant results in both test might be an indication of a publication bias of the results. These methods have been developed particularly for meta-analysis studies (15).

3. Results

There are 3,099 blood samples in the selected 11 studies from 1995 to 2014, 1,837 of them BVD positive, 1,790 are IBR positive. The prevalence of BVD and IBR ranged between 14 % - 81 % and 43 %-72 % respectively. The result and effects of the studies were provided in the forest plot, the pooled odds ratio was calculated as 1.13 (Figure 1).

The heterogeneity thresholds, according to The Cochrane hand book (14), was high in this study, the heterogeneity level (Test for heterogeneity: I^2 = 99.05, X^2 (10) = 265.74, (p-value = 0) proved that the difference between the studies are significant and considerable heterogeneity. The 1.13 odds ratio shows that BVD and IBR results are close to each other, but slightly tends to BVD. The different methods that used in this study has been shown in the table 2 and 3, and the results of these methods had similar results.

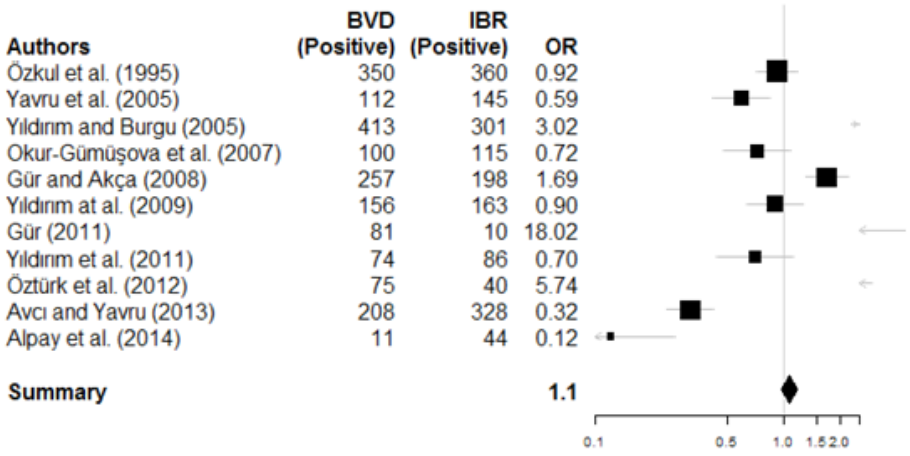

Figure 1: The Forest Plot
Şekil 1: *Orman grafiği*

Table 1: Meta-analysis table of BVD and IBR
Tablo 1: *BVD ve IBR Meta analiz tablosu*

The Authors	BVD Positive	Total Samples	IBR Positive	Total Samples	Odds Ratio	%95 CI lower limit	%95 CI upper limit
Ozkul et al. – 1995 (16)	350	538	360	538	0.92	0.72	1.18
Yavru et al. – 2005 (17)	112	254	145	254	0.59	0.42	0.84
Yildirim and Burgu – 2005 (18)	413	506	301	506	3.02	2.27	4.03
Okur-Gumusova et al.–2007 (19)	100	188	115	188	0.72	0.48	1.09
Gur and Akca – 2008 (20)	257	452	198	452	1.69	1.3	2.2
Yildirim et al. – 2009 (21)	156	265	163	265	0.9	0.63	1.27
Gur – 2011 (22)	81	139	10	139	18.02	8.71	37.25
Yildirim et al. – 2011 (23)	74	140	86	140	0.7	0.44	1.13
Ozturk et al. – 2012 (24)	75	92	40	92	5.74	2.94	11.19
Avci and Yavru – 2013 (25)	208	450	328	450	0.32	0.24	0.42
Alpay et al. – 2014 (26)	11	75	44	75	0.12	0.06	0.27

Table 2: Mantel-Haenszel Method Analysis confidence intervals (95 % CI)
Tablo 2: *Mantel-Haenszel Yöntemine göre güven aralıkları (% 95 GA)*

	No of Studies	Sum Odds ratio	Lower limit	Upper limit
Fixed Effects	11	1.06	0.96	1.18
Random Effects	11	1.15	0.65	2.02

In order to estimate asymmetry of data Begg's and Egger's tests can be used, and the p-value less than 0.05 implicates publication bias. The results of this study, Begg-Mazumdar: Kendall's tau = -0.0182, p = 1.0000, Egger's regression: test for funnel plot asymmetry: z = 0.6934, p = 0.4881. In addition to that symmetrical plot in the Figure 2 shows absence of publication bias. Nevertheless, the low statistical power should be bear in mind.

Table 3: Peto Method Analysis confidence intervals (95 % CI)
Tablo 3: *Peto Yöntemine göre güven aralıkları (% 95 GA)*

	No of Studies	Sum Odds ratio	Lower limit	Upper limit
Fixed Effects	11	1.07	0.96	1.18
Random Effects	11	1.11	0.63	1.97

The publications used in this study took place in different regions and population, the main reason of the high heterogeneity can be this difference. The different farms may have different results as well; however, the results showed the existence of two diseases in any case. The random effect model used because of the high heterogeneity.

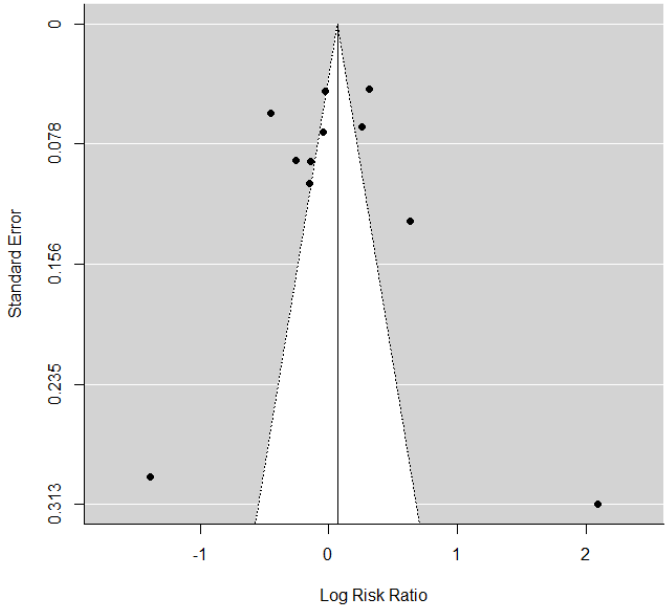

Figure 2: Funnel Pilot
Şekil 2: *Huni grafiği*

4. Discussion and Conclusion

Together with Bovine Viral Diarrhoea and Infectious Bovine Rhinotracheitis are two most important viral abortive diseases in cattle (5). Both agents can affect the genital system and are spread by coitus. They cause fertility problems, abortion and stillbirth without any clinical symptoms. The analysis of this project proved that the antibodies to both viruses exist in the same blood serum in the cattle of Turkish farmers.

Except Scandinavian and some central European countries, IBR and BVD prevalence is high in some part of Europe, for example in Ireland, BVD herd prevalence was more than 30 %, and IBR was between 10 and 15 % (27). In Croatia, the prevalence is higher (BVD 85.8 %, IBR 79.2 %) in farms with reproductive disorders (28).

Past studies and this systematic review showed that both viruses have been circulating in Turkey. Therefore, in order to prevent reproduction losses and improve the livestock industry, control and awareness schemes about the diseases should be planned by the competent authorities and universities. Education of farmers and supporting artificial insemination should take place. At the planning phase of these non-zoonotic diseases, the costs of eradication and the possibility of achieving a disease-free status should be considered. Other factors that should be considered are food safety and animal welfare. Besides the financial losses, the mucosal disease is painful for cattle.

Control and eradication programs should follow some similar steps. For instance, a BVD control and eradication program in Denmark started in 1994 with some pilot projects on a voluntary basis. After that, according to the results of this project some legislation took force. Positive herds are tested, test methods improved, persistent animals detected and culled. The motivation of farmers was increased by meetings with farmers and livestock organisations. With this approach, from 1994 to 1999, the prevalence of BVD declined from 39 % to 9 %. It was eradicated in 2014 (29).

Finally, it should be noted that the reason of high seropositivity of BVD and IBR may be a bias caused by the combination vaccines used by farmers. This fact should be clarified by further studies.

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