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A Meta-Analysis of the Effect of Probiotics Administration on Growth Performance of Suckling Calves in Iran

Review Article

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ABSTRACT

Probiotics have been shown to have beneficial effect on the growth performance of newborn animals. However, the results are inconsistent, especially in Iran. A meta-analysis was carried out to evaluate the effects of probiotics on dry matter intake (DMI), daily weight gain (DWG) and feed efficiency (FE) in suckling calves using data from the studies conducted in Iran. The literature review resulted in 13 documents including 6 and 5 papers written in English and Farsi respectively, as well as 2 papers presented in national conferences. Random effect meta-analysis was performed to evaluate the effect of probiotics on growth performance of the suckling calves using STATA statistical software on 8 papers that were identified as suitable for the objective of this study. Univariate and multivariate meta-regression analyses were also performed to evaluate the effects of experimental period (≤8 weeks *vs.* >8 weeks), gender of calf (male *vs.* female), type of probiotic (bacteria *vs.* a combination of yeast and bacteria), and probiotic administration manner (in milk *vs.* in starter) on the study outcomes. The results of meta-analysis showed no significant effect of probiotics on DMI. However, a significant difference was identified by subgroup meta-analysis between the experimental period subgroups for the effect of probiotics on DMI. Probiotics administration increased DWG of suckling calves by 47 g/day (P<0.01). The effect of probiotics on feed efficiency was not significant. The results indicated that the probiotic administration may improve DMI and DWG in suckling calves.

KEY WORDS heterogeneity test, meta-regression, random effect size.

INTRODUCTION

Successful calf raising is an investment in the future of dairy herds and is critical to establish an optimal replacement policy. Health and subsequent productivity of suckling calves may be negatively affected by intestinal diseases which are potentially high in intensive rearing systems (Rosmini *et al.* 2004). Antibiotics have been widely used as feed additives to solving this challenge. However, the use of antibiotics is associated with the development of antibiotic-resistant. Therefore, scientists and practitioners are constantly looking for new alternative feeds or additives that can improve the health, production and profitability of animals (Bryszak *et al.* 2019; Mravčáková *et al.* 2019). Probiotics are one of the supplements that are being successfully tested (Zhang *et al.* 2016; Huang *et al.* 2019). As an alternative of antibiotics, probiotics are live microbial feed additives that beneficially affect the host animal, generally by improving or restoring the gut flora (Fuller, 1989). Although the beneficial effects of probiotics on calf heath and performance have been wildly investigated, the results are inconsistent. Under the dairy calves rearing condition in

Iran, for instance, probiotics administration in suckling calves improved growth rate (Mohamadi-Roodposhti and Dabiri, 2012), feed intake (Seifzadeh *et al*. 2017) and/or feed conversion ratio (Moslemipur *et al*. 2014). In contrast, Bakhshi *et al*. (2006), Bayatkouhsar *et al*. (2013) and Hosseinabadi *et al*. (2013) reported no effect of probiotics on growth performance of young calves. This contradiction in the results could be attributed to various factors such as type of probiotic, manner of probiotic delivery to calves and duration of experimental period. On the other hand, there is a regional variation for pre-weaning calf mortality and growth, primarily due to the regional conditions and calf rearing system (Moran, 2011). Therefore, a combination of local study results may be helpful to decide on the use of probiotics as a growth promoter for suckling calves in a certain region, such as Iran with 842000 Holstein cows on commercial dairy farms.

Meta-analysis is a statistical technique for combining data from multiple studies on a particular topic to systematically assess previous research studies and derive conclusions about that body of research. Moreover, meta-regression analysis may also be used to investigate the factors contributing to the heterogeneity across studies (Lean *et al*. 2009). This study was aimed to meta-analysis of the effect of probiotics on growth performance of suckling calves in Iran using data from the local studies.

MATERIALS AND METHODS

Literature review, outcome evaluation and data extraction

Literature review was conducted on the basis of a search in Google Scholar, CIVILICA, ScienceDirect, Magiran, Islamic World Science Citation, and Scientific Information Database using combinations of keywords: "probiotic", "calves or calf", "yeast", "protexin" and "Iran" both in English and Farsi. The keywords were also individually searched in the local scientific journals. The search was not restricted to peer-reviewed journals and it included journal articles and conference proceedings. The papers that reported the effect of probiotics feeding on the growth performance of suckling calves were selected for this study. All studies to be included in the meta-analysis were screened using the following standardized criteria: studies should have 1) conducted in Iran, 2) evaluated the effect of probiotics on suckling calves, 3) included at least one control and one treated (probiotic) group, and 4) reported at least one performance parameter e.g. starter dry matter intake (DMI), daily weight gain (DWG) and/or feed efficiency (FE) with a measure of variance (standard error or standard deviation). Because an overall standard error was reported in all of the included studies, no conversion was required to estimate standard error.

The mean differences in DMI (kg/day), DWG (kg/day) and FE (DMI:DWG) between treated and control group were used as the outcomes. If the studies reported these outcomes in any other measurement (e.g. g/day), the outcomes were transformed to kg/day. In addition to the outcomes, gender of calves, duration of experiment (≤8 weeks and >8 weeks), type of probiotic (yeast, bacteria, and a composition of yeast and bacteria), and strategy of probiotic delivery (in milk and in starter) data were also extracted from the trials for sub-group analysis.

Meta-analysis

The extracted data including number of observation, means and standard error for both control and treated groups was subjected as continuous data to random and fixed effects meta-analyses using "metan" command of Stata/SE software (Stata 14.1, Stata Corporation, Col-lege Station, TX, USA) to evaluate the effect of probiotics on DMI, DWG and FE of suckling calves. A random effects meta-analysis considers the variation between studies and assumes that there is a normal distribution for the study effects and the variance of the distribution is estimated from the data (Rabiee *et al*. 2012). The variance for random effects model was estimated using DerSimonian and Laird invers variance method (Higgins and Thompson, 2002) and the heterogeneity statistic Q was used to determine if there was significant variability between studies (Lean *et al*. 2009; Rabiee *et al*. 2012). Because a significant P-value (i.e. <0.05) for the Q statistic was observed, the results from the random-effects model including random effect size (standardized mean difference (SMD)), 95% confidence interval and P-value are reported in this manuscript. Moreover, weighted mean difference (WMD) was measured as an unadjusted difference between control and treated group. The results of sub-group meta-analysis are presented as forest plots.

Meta-regression analysis

Meta-regression analysis was performed on SMD and corresponding standard error values of each compression as dependent variable using "metareg" command of STATA/SE software to explain the sources of heterogeneity that may have influenced study outcomes. In this study, gender of calf, duration of experiment, type of probiotic, and strategy of probiotic delivery were investigated as sources of heterogeneity between the studies. Each source of the heterogeneity was separately subjected to the univariate meta-regression analysis and then multivariate meta-regression analysis were performed for the sources with a P-value of <0.3 (Mirzaei-Alamouti *et al*. 2015). The heterogeneity source(s) was determined using a step-by-step backward elimination procedure with a significance threshold of 0.05.

RESULTS AND DISCUSSION

A total of 13 documents including 6 and 5 papers written in English and Farsi respectively, as well as 2 papers presented in national conferences were identified. Of the 13 studies identified by literature review, 8 potential studies were eligible for inclusion in this meta-analysis. Out of the 8 studies that met inclusion criteria, 10, 9 and 7 comparisons were usable in the meta-analysis on DMI, DWG and FE, respectively. Details of the studies and comparisons are presented in Table 1. Meta-analyses with too few studies (≤7 studies) are common (Michael *et al.* 2019). For example, Seide *et al.* (2019) reported that 31 out of the 40 meta-analyses (~77%) from recent reviews published by the German Institute for Quality and Efficiency in Health Care included only 2 or 3 studies. Turner *et al.* (2013) concluded that when at least two adequately powered studies are available in meta-analyses, underpowered studies often contribute little information. In the present study, at least two well powered studies were included to the meta-analysis (Bakhshi *et al.* 2006; Hosseinabadi *et al.* 2013).

Feed intake

The results of meta-analysis for 10 comparisons from 6 trials showed that the probiotics administration had no significant effect (P=0.085) on DMI of suckling calves (Table 2; Figure 1).

However, a significant heterogeneity was observed across studies (P=0.018, I^2=58.5%). Based on the univariate meta-regression analysis, calf gender (P=0.182) and duration of experiments (P=0.018) were identified as sources of heterogeneity. Furthermore, P-value of the multivariate meta-regression analysis for these two sources was 0.043 (Table 3).

This results suggest that the positive impact of probiotics on DMI of suckling calves is associated to gender of calve as well as duration of experimental period. Gender subgroup meta-analysis showed a numerically higher DMI in male compared to female calves. As shown in Figure 2, DMI was not affected by probiotics administration when feed intake was measured for ≤ 8 weeks. However, the positive effect of probiotics on DMI was more obvious in the studies where feed intake was measured for more than 8 weeks.

The solid feed intake in young calves is a function of rumen development as well as many physiological adjustments at the gut, hepatic, and tissue levels (Khan *et al.* 2011). Probiotics have been shown to improve rumen development in young ruminants (Kmet *et al.* 1993; Laborde, 2008).

The findings of the present meta-analysis, however, suggest that the probiotics have no significant effects on rumen development at pre-weaning stage, but may improve post-weaning solid feed intake.

Table 1 Details of the experiments used in meta-analysis

Literature ID (reference)	Source	N	Outcom DMI	Outcom DWG	Outcom FE	Gender	Duration	Probiotic type	Administration manner
Bakhshi *et al.* (2006)	*Intlian J. Dairy Sci.*	10	+	+	+	Female and male	≤ 8 weeks	Bacteria	Milk
Bayatkouhsar *et al.* (2013)	*Anim. Feed. Sci. Technol.*	8	+	+	-	Female	≤ 8 weeks	Bacteria	Milk
Bayatkouhsar *et al.* (2013)	*Anim. Feed. Sci. Technol.*	8	+	+	-	Female	≤ 8 weeks	Bacteria	Milk
Mohamadi-Roodposhti and Dabiri, (2012)	*Asian-Australasian J. Anim. Sci.*	8	+	+	-	Female	≤ 8 weeks	Bacteria and yeast	Milk
Seifzadeh *et al.* (2017)	*Italian J. Anim. Sci.*	5	+	+	+	Male	> 8 weeks	Bacteria and yeast	Milk
Seifzadeh *et al.* (2015)	*Conference*	5	+	-	-	Male	> 8 weeks	Bacteria and yeast	Starter
Hossein Abadi *et al.* (2013)	*Res. Anim. Prod.*	10	+	+	+	Female	≤ 8 weeks	Bacteria and yeast	Starter
Hossein Abadi *et al.* (2013)	*Res. Anim. Prod.*	10	+	+	+	Female	≤ 8 weeks	Bacteria and yeast	Milk
Hosseini *et al.* (2017)	*Conference*	10	+	+	+	Female	> 8 weeks	Bacteria and yeast	Starter
Hosseini *et al.* (2017)	*Conference*	10	+	+	+	Female	> 8 weeks	Bacteria and yeast	Starter
Moslemipur *et al.* (2014)	*J. Rumin. Res.*	4	-	-	+	Male	≤ 8 weeks	Bacteria and yeast	Milk

DMI: dry matter intake; DWG: daily weight gain and FE: feed efficiency.

Table 2 Meta-analysis of the effect of probiotic on dry matter intake (DMI), daily weight gain (DWG) and feed efficiency (FE) of suckling calves

Outcome	N experiments (N comparisons)	SMD		WMD (95% CI)	Heterogeneity test			
		Random effect (95% CI)	P-value		Chi-squares	Df	I-squared (%)	P-value
DMI (kg/day)	6 (10)	0.328 (-0.045 to 0.700)	0.085	0.043 (-0.162 to 0.249)	12.59	9	58.5	0.018
DWG (kg/day)	6 (9)	0.487 (0.137 to 0.819)	0.006	0.047 (-0.003 to 0.098)	8.89	8	10.0	0.352
FE (DMI:DWG)	5 (7)	0.088 (-0.452 to 0.628)	0.750	- 0.037 (-0.096 to 0.021)	11.66	6	48.5	0.070

SMD: standardized mean difference; CI: confidence interval; WMD: weighted mean difference and Df: degree of freedom.

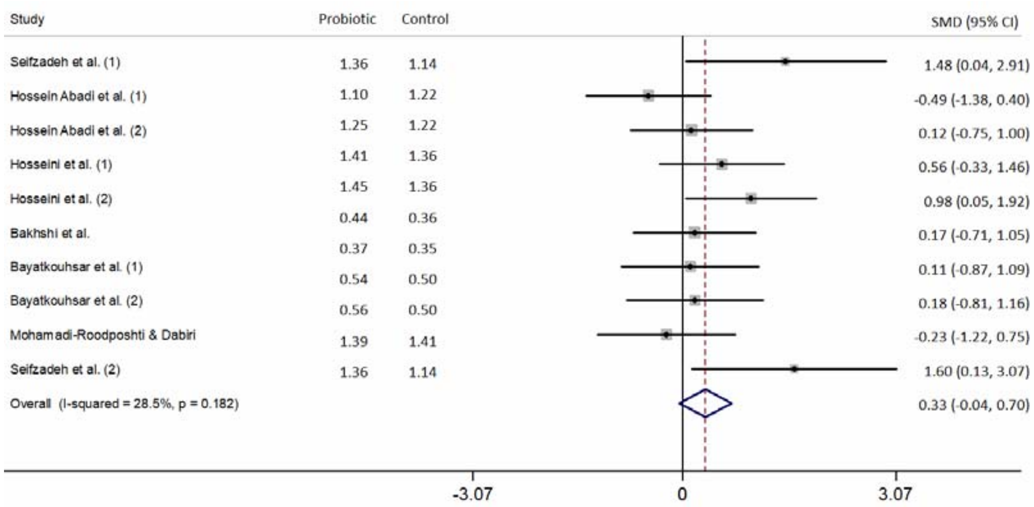

Figure 1 Means and forest plot of standardized mean differences (SMD) with their 95% confidence interval (95% CI) for the random effect of probiotic on dry matter intake of suckling calves

Table 3 Meta-regression of factors may have influenced the effect of probiotic on dry matter intake (DMI), daily weight gain (DWG) and feed efficiency (FE) in suckling calves

Outcome (subgroup)[1]	Coefficient (95% CI)	Standard error	P-value	
			Test of each covariate	Joint test for all covariates
DMI				
(Gender)	0.639 (-0.370 to 1.649)	0.438	0.182	0.043
(Duration)	1.010 (0.227 to 1.793)	0.339	0.018	
DWG				
(Probiotic type)	-0.412 (-1.207 to 0.384)	0.337	0.261	0.263
(Duration)	0.509 (-0.336 to 1.355)	0.358	0.197	
FE				
(Probiotic type)	-0.766 (-2.023 to 0.491)	0.416	0.178	

[1] Gender: male *vs.* female; Duration: ≤ 8 weeks *vs.* > 8 weeks; Probiotic type: bacteria *vs.* bacteria and yeast.
CI: confidence interval.

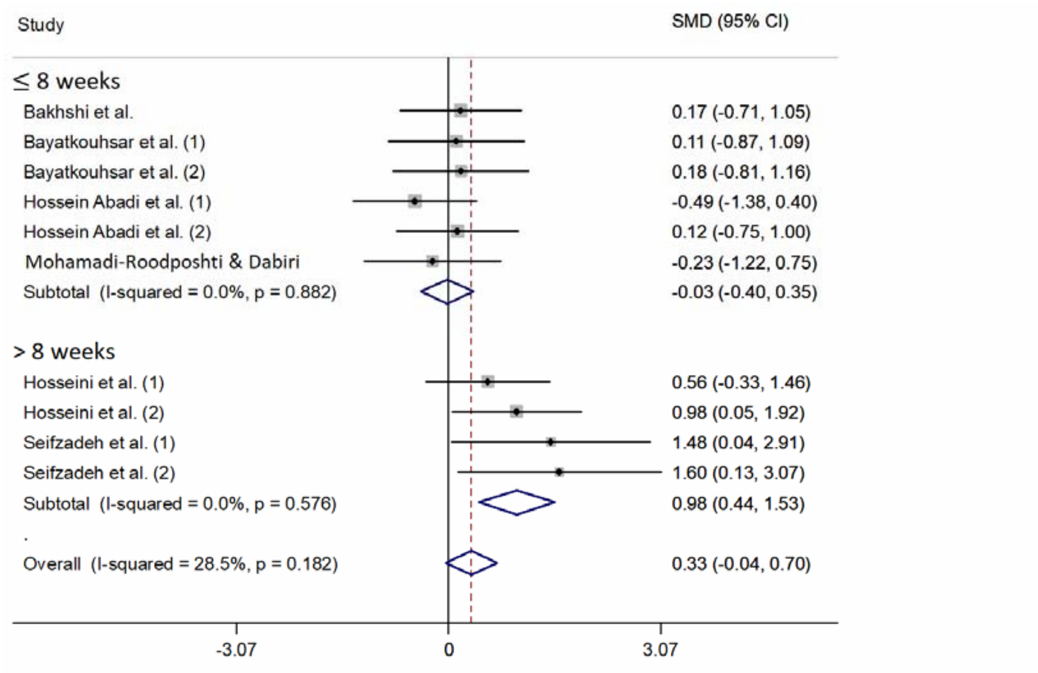

Figure 2 Forest plot of standardized mean differences (SMD) with their confidence interval (95% CI) for the random effect of probiotic on dry matter intake of suckling calves in two experiment period groups (≤8 weeks and >8weeks)

Daily weight gain

Meta-analysis was performed for 9 comparisons from 6 trails to evaluate the effect of probiotics on DWG of suckling calves (Figure 3). Standardized mean difference (95% CI) and P-value were 0.482 (0.137 to 0.819) and 0.006, respectively. Furthermore, a weighted mean difference of 0.047 (-0.003 to 0.098) was also detected between probiotics and control treatments for DWG (Table 2).

In a similar meta-analysis, Frizzo *et al.* (2011) reported a significant positive effect of probiotics administration on weight gain of young calves using 36 comparisons from 21 independent trials.

These authors, however, suggested that the probiotics had no significant effect on growth rate of whole milk fed calves or when the duration of the experiment was < 45 days.

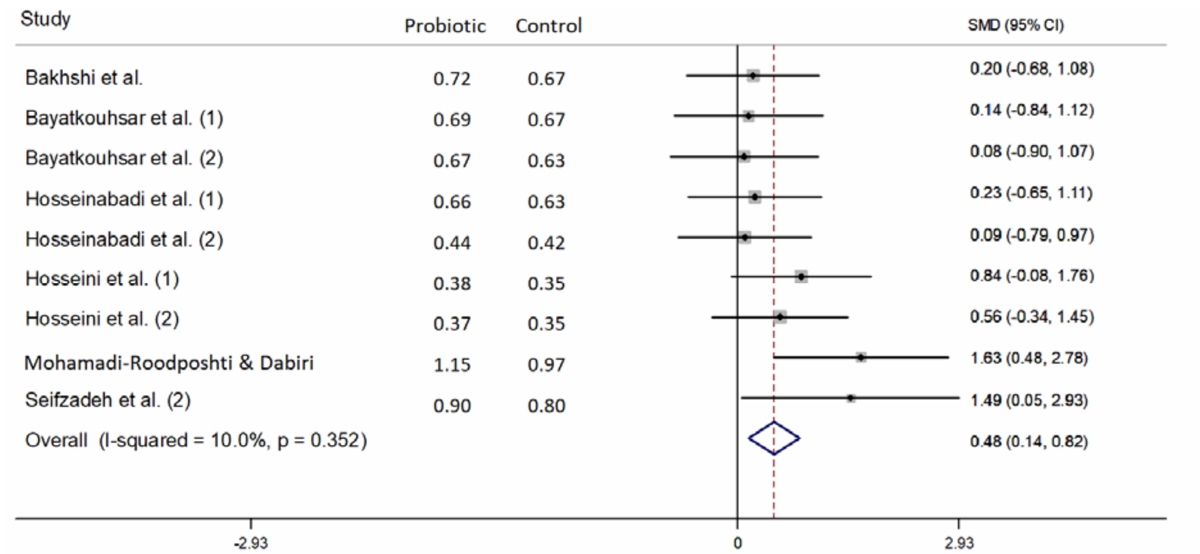

Figure 3 Means and forest plot of standardized mean differences (SMD) their confidence interval (95% CI) for the random effect of probiotic on daily weight gain of suckling calves

In the present meta-analysis, all included experiments provided whole milk to the calves and the heterogeneity across studies was non-significant (P=0.352, I^2=10.0%) for DWG. Although P-values for both type of probiotic (P=0.261) and duration of experiment (P=0.197) in univariate meta-regression analysis were less than the chosen significance level of 0.3, multivariate meta-regression analysis showed no correlation between these variables and probiotics administration for DWG (P=0.263). These findings are in agreement with heterogeneity test results and suggest that the positive effect of probiotics on DWG of suckling calves is independent of the type of probiotic, duration of experiment, gender of calf, and strategy of probiotic delivery. Furthermore, an average improvement of 47 g in DWG is expected by probiotics administration in suckling dairy calves.

Feed efficiency

As shown in Table 2, a weighted difference mean of -0.037 (-0.096 to 0.021) was detected for FE. Because the efficiency of feed intake in all included experiments was measured as feed conversion ratio (DMI:DWG), the negative value indicated an improvement in feed efficiency by probiotic administration.

However, the results of the random effect meta-analysis showed non-significant effect of probiotics on FE of suckling calves (P=0.570). Heterogeneity was not significant across studies (P=0.07). No significant correlation was also observed between heterogeneity sources and probiotic for FE. Although Frizzo *et al.* (2011) suggested that the probiotics administration improved FE in young calves, these authors, however, noted that probiotics had no significant impact on FE when the calves fed whole milk that is in agreement with our results.

CONCLUSION

The results of the present meta-analysis indicated that probiotics may improve daily weight gain of suckling calves by 47 g under the rearing conditions in Iran. This effect of probiotics on DWG is, however, independent of calf's gender, probiotic type, experimental period and strategy of probiotic delivery. Moreover, the results suggest a positives impact of probiotics on post-weaning DMI of dairy calves. However, no significant effect of probiotics on feed efficiency was identified by the present meta-analysis.

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