american physiological society
ADVANCES IN PHYSIOLOGY EDUCATION

Adv Physiol Educ 48: 155–163, 2024.
First published January 18, 2024; doi:10.1152/advan.00182.2023

EDUCATION RESEARCH

Game-based learning enhances students' understanding of endocrine physiology in veterinary medicine

Marcos Vinícius Ramos Afonso,[1] Rodrigo Braga Lopes,[2] Eric Francelino Andrade,[2] and Luciano José Pereira[2]

[1]*Veterinary Sciences Department, Universidade Federal de Lavras (UFLA), Lavras, Minas Gerais, Brazil; and* [2]*Health Sciences Department, Universidade Federal de Lavras (UFLA), Lavras, Minas Gerais, Brazil*

Abstract

Endocrine physiology is a complex subject for students. Game-based learning (GBL) and case-based learning (CBL) are active methodologies that are widely used because of their potential for motivation and greater proximity to the reality of modern students. We evaluated the effectiveness of GBL and CBL among veterinary medicine students compared with a control group using peer tutoring. Students ($n = 106$) from two institutions volunteered to participate in this study. The participants were submitted to a pretest questionnaire and subsequently were divided into three paired groups by their performance on the pretest exam: *1*) traditional class + peer tutoring, *2*) traditional class + GBL, and *3*) traditional class + CBL. After the students completed the activities, their performance was once again evaluated by applying a new test with the same initial 10 questions and another set of 10 different questions. The students' perceptions and satisfaction with the methodologies and learning strategies were assessed. Anxiety was assessed with the State-Trait Anxiety Inventory before and after the conventional class and after the active methodologies. The GBL group significantly improved their correct answers compared with the baseline ($P < 0.05$), with no significant difference from CBL and peer tutoring. Anxiety levels did not differ regardless of the time of evaluation or the teaching methodology applied. GBL promoted a greater perception of the stimulus for self-study and problem-solving ability and contributed to the development of group dynamics compared with the group who received CBL ($P < 0.05$). In conclusion, GBL showed better results than peer tutoring and CBL.

NEW & NOTEWORTHY We compared the supplementary use of game-based learning, case-based learning, and peer tutoring in the study of endocrine physiology by veterinary students and observed a slight advantage for game-based learning over the other two methodologies. The game was developed by the authors and is an unprecedented tool that can prove useful to improve knowledge acquisition in students of veterinary medicine. Thus, game-based learning is an effective supplementary teaching strategy.

active learning methods; endocrinology; student perception; veterinary education

INTRODUCTION

Animal/veterinary physiology is a mandatory basic subject in the curriculum of veterinary medicine courses. Among the organ systems studied, endocrinology is the study of hormones and their synthesis, secretion, mechanisms of action, and impact on homeostasis. Since there are several hormones with different receptors in different target tissues with multiple actions in the organism, it is common for students to consider endocrine physiology difficult (1).

In most educational institutions, the methodology used in physiology disciplines is passive, consisting of expository classes/lectures where the teacher is responsible for transmitting knowledge and students participate only as listeners who acquire knowledge passively (2). This teaching methodology has been considered deficient in many cases because it generates low engagement and motivation and, consequently, low retention of content (3). Teaching improvement techniques are needed to increase student motivation (4). In this context, active teaching methodologies emerge as alternatives that make the student the protagonist of his or her own learning (5).

Among active methodologies, game-based learning (GBL) and case-based learning (CBL) can be highlighted. GBL is a didactic method that involves the use of games or gamified elements as part of the educational process to engage and educate students (6–8). These games may be analog games that use cards and boards or electronic/digital games that use software and applications (9). GBL is one of the preferred methods for the teaching/learning process among students because it favors the study of content in a dynamic and interactive way (10). Another widespread methodology is case-based learning (CBL), which uses clinical cases and questions to instigate and direct students' reasoning to understand and solve problems (11). During case studies,

Correspondence: L. J. Pereira (lucianojosepereira@ufla.br).
Submitted 5 September 2023 / Revised 11 January 2024 / Accepted 15 January 2024

students interact and discuss in small groups, providing an exchange of knowledge between participants and helping them to better understand and retain knowledge (12).

The literature reports that both GBL and CBL can provide greater dynamism, interaction, and participation among students and can support more active behavior, greater understanding of content, and increased knowledge retention (13, 14). However, although several studies have been conducted in recent years using active methodologies to improve higher education about endocrine physiology in health courses (2, 15, 16), research that aims to understand the study of endocrine physiology in veterinary medicine is still scarce.

The understanding of endocrine physiology facilitates the understanding of several pathophysiological mechanisms of animal diseases as well as the identification of clinical signs, facilitating diagnosis and directing more assertive treatment. Thus, the effective learning of physiology is crucial for students' qualification for professional life (17). However, because of its complexity, the content of endocrine physiology can be stressful for students and may cause the emergence of anxiety (18, 19). Anxiety is associated with poor attention span and assimilation/memory deficits (20). In contrast, active methodologies are promising teaching strategies that can support the understanding of physiology by enabling greater dynamism and learning with reduced levels of anxiety (2, 18).

Given the challenges associated with the study of endocrine physiology and the difficulties students encounter in comprehending this subject matter, our primary aim was to compare the pedagogical efficacy of game-based learning (GBL) and case-based learning (CBL) against peer tutoring on the academic performance, satisfaction, and anxiety levels of undergraduate students in the field of veterinary medicine. Additionally, we sought to develop and implement a board game centered on endocrine physiology.

MATERIALS AND METHODS

The present study was approved by the Human Research Ethics Committee of the Federal University of Lavras–UFLA (CAAE 51344321.4.0000.5148). All volunteers completed a Free and Informed Consent Form. The study included students from two veterinary medicine courses at private higher education institutions in the state of Minas Gerais in the southeast region of Brazil who were enrolled in the veterinary physiology discipline between March and November 2022. *Institution 1* accommodates 50 students per class in the daytime on-campus program, whereas *institution 2* offers on-campus courses with 60 available slots for both daytime and evening modes. Students from both institutions (approximately $n = 150$) were approached in the classroom after consent was obtained from the institution and the teacher in charge, and the purpose and objective of the research were explained to them.

Initially, 106 students consented to participate (*institution 1*: $n = 20$; *institution 2*: $n = 86$). The research team administered a questionnaire before initial exposure to the content of endocrine physiology that comprised 10 objective questions adapted from the *Textbook on Medical Physiology* (21). The questionnaire was intended to assess students' level of prior knowledge about endocrine physiology. Subsequently, in each institution the total number of volunteers participating in the study was counted, and they were randomly distributed (without identification) in similar numbers into three groups considering their performance on the pretest to construct paired groups. At *institution 1*, each group had 6 or 7 participants, whereas at *institution 2*, each group had 28 or 29 members. At the beginning of the study, the group that received traditional class + peer tutoring had 35 participants, the group that received traditional classroom + GBL teaching also had 35 participants, and the group that received traditional classroom + CBL teaching had 36 participants. Subsequently, according to the score obtained by each student on the questionnaire, the participants were redistributed in subgroups of three or four students on an equal basis considering the number of correct answers to ensure the homogeneity of the groups.

Lecture-style classes were taught in person by the professor in charge at each institution. In both institutions, the responsible professors held doctoral degrees and had a minimum of 5 years of experience teaching physiology. The endocrine physiology content taught at different institutions was similar and followed the same order to standardize this stage of the study. In these classes, which lasted 240 min, the content was taught orally with a PowerPoint presentation and the students subsequently went through the evaluation period according to the specific schedule of the discipline. In this way, active teaching methodologies were carried out after evaluations, with peer tutoring, GBL, and CBL activities used as complementary methods in extraclass hours. Each modality of teaching methodology (peer tutoring, CBL, and GBL) was used for 140 min, as shown in Table 1. All teaching methodologies were developed and revised by two physiology specialists with >10 years of teaching experience (E.F.A. and L.J.P.), using the *Textbook of Medical Physiology* (18) as supporting material. Additionally, the two lead instructors of the classes assessed at both institutions were consulted for suggestions before the commencement of the study. Student participation was entirely voluntary, with no disruption to the evaluation of the subject. Students were at liberty to withdraw from participation at any point without incurring any penalties. The sessions for the employed methodologies were scheduled with the groups during the students' available extra hours in the same weeks as the regular classes conducted by the lead instructor.

Table 1. *Distribution of stages and time allocated for carrying out the activities*

Stage	Time	Activities
1	50 min	Pretest + State and Trait Anxiety Inventory
2	240 min	Expositive lectures about endocrine physiology (hypothalamus, pituitary, thyroid, parathyroid, pancreatic, and adrenal) + State and Trait Anxiety Inventory
3	140 min	Additional methodologies (peer tutoring, case-based learning, and game-based learning)
4	50 min	Posttest + satisfaction and perception of methodologies questionnaire + learning strategies questionnaire + State and Trait Anxiety Inventory

Peer Tutoring

The study participants allocated to the peer tutoring group were asked to self-study, and a designated medical student (tutor) was available to answer questions as needed. Peer tutoring was conducted in all institutions always by the same medical student previously selected by the researchers (duly approved in the physiology discipline at their teaching institution) and a doctoral student who was the moderator. The tutor helped the study participants on occasions when there were doubts and questions related to the content. This strategy was used as a placebo to provide the same additional interaction time with the endocrinology content as the groups who received the other methods.

Case-Based Learning

The students allocated to the case-based learning (CBL) group received five clinical cases related to the subject of endocrinology, involving hyperthyroidism, diabetes mellitus, hypoadrenocorticism, hyperparathyroidism, and acromegaly (Supplemental Table S1; available at https://doi.org/10.6084/m9.figshare.24431467). The cases were prepared in the form of medical records containing the main complaint, anamnesis, physical examination, complementary tests, and diagnosis. Each clinical case contained discursive questions, and the students discussed them collaboratively to solve the questions in groups. During the discussion, the participants had access to the internet. The tutors also helped the study participants during the case discussion.

Game-Based Learning

The game was developed by the researchers based on an interactive activity composed of a snakelike board involving questions related to the physiology of the endocrine system, such as hormonal functions, secretory cells, mechanism of action, and control of secretions. To play the game, a board, dice, pawns (pins), and cards were used.

During the game, a competition was held between the participants, who randomly gathered in groups ($n = 3$ or 4) and threw the dice. Interaction among students was competitive between group members during the game. The participant who rolled the highest value on the dice started the game. During the performance, each student threw the dice, and as the pawns stopped on specific squares on the board questions were removed and answered by the player, and the player's colleagues evaluated whether the answer was correct. If the answer was correct, the participant could play again; otherwise, another student played. The tutors also helped the study participants in organizing the game process.

The questions used in the game were organized in the form of cards according to the level of complexity: beginner (easy), moderate (intermediate), and hard (expert). The board was A3 size (42 × 29.5 cm), and the cards with the questions were 5 cm × 7 cm. The game was composed of 50 boxes, of which 15 were for questions (5 beginners, 5 apprentices, and 5 experts), 15 promoted movement dynamics (advance or return boxes), and 20 were neutral boxes [Supplemental Figs. S1 (available at https://doi.org/10.6084/m9.figshare.24431473) and S2 (available at https://doi.org/10.6084/m9.figshare.24431479).

Assessment of Students' Opinion and Satisfaction with Active Methodologies

After completing the complementary sessions, the students who participated in the GBL and CBL groups completed a printed questionnaire about their perception, satisfaction, and opinion of the methodologies employed. The questionnaire was adapted from Gade and Chari (2), Franco-Mariscal et al. (21), and Cardozo et al. (5, 22) and contained eight objective questions. The questions were answered with a Likert scale ranging from 1 to 5, with 1 indicating "I totally disagree" and 5 indicating "I totally agree."

Assessment of Individual Study Strategies

The individual study strategies used by the students to study endocrine physiology were evaluated with a printed questionnaire composed of 12 questions adapted from Maciel et al. (23), which was applied after the additional teaching strategies were conducted. This questionnaire had a Likert scale classified in grades from 1 to 5 for the behavior performed in each question, with 1 indicating behavior never performed and 5 indicating behavior always performed.

Assessment of Anxiety Scores (State-Trait Anxiety Inventory)

Anxiety was assessed with the Brazilian Portuguese version of the State-Trait Anxiety Inventory (STAI) proposed and validated by Spielberger et al. (24). This instrument has 40 questions: 20 are related to trait anxiety (TA), and 20 are related to state anxiety (AE). Each question consisted of a Likert scale with four possible answers: "very much," "quite a bit," "a little," and "absolutely not." The quantification of the level of anxiety was determined through the sum of the values obtained in the questions for both AE and TA. To classify anxiety levels, cutoff points were used: 20 to 40 was defined as "low anxiety," 41 to 60 was defined as "moderate anxiety," and values between 61 and 80 were defined as "high anxiety" (25). Participants answered the STAI at three times: before attending traditional classes, after watching all the content of traditional classes, and after activities involving active learning methodologies.

Evaluation of Academic Performance

After the methodologies were finalized, a questionnaire was administered to the students to assess their learning. The questionnaire included 20 questions, including the same 10 questions from the pretest randomly distributed with 10 new questions adapted from the *Textbook of Medical Physiology* (26). To determine the students' retained knowledge and compare it with prior knowledge, only the 10 applied pretest questions were used.

To prevent potential interference from the duration of content exposure and the cumulative effect of employing multiple teaching modalities for the same content, the present study did not adopt a crossover design. However, after the data collection all participants were granted access to the methodology of the other groups to ensure exposure to all techniques, thereby addressing ethical considerations.

Statistical Analysis

The data were analyzed with inferential statistics consisting of the mean, median, standard deviation, and standard error

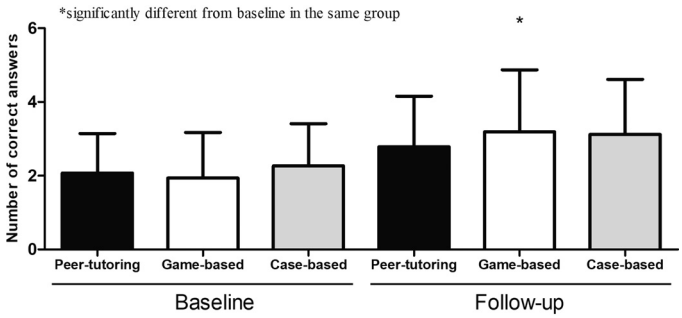


Figure 1. Number of correct answers on multiple-choice objective questions among veterinary medicine students who received a didactic activity involving a traditional lecture associated with peer tutoring, game-based learning, or case-based learning. Wilcoxon test at 5% significance for paired groups; Kruskal–Wallis test at 5% significance to compare between modalities.

of the mean. Additionally, the Kolmogorov–Smirnov normality test was performed. Comparison of the students' performance before (pretest) and after (posttest) the application of the methodologies (number of correct questions) was performed with the Wilcoxon test for paired groups, and the comparison between the three didactic modalities was performed with the Kruskal–Wallis test. The trait and state anxiety scores were analyzed with the Friedman test for comparisons between different moments in the same group and the Kruskal–Wallis test for comparisons of scores between different groups at the same moment. The frequencies of use of learning strategies were compared by the Kruskal–Wallis test, whereas the level of satisfaction between the GBL and CBL methodologies was analyzed with the Mann–Whitney test. The significance level was $P < 0.05$, and the software used was GraphPad Prism 5 (GraphPad Software version 5.01, San Diego, CA).

RESULTS

Initially, 106 students responded to the pretest. Of these students, only 65 completed all tasks properly and participated until the posttest. At *institution 1* 20 students completed all stages, whereas 45 participants completed all stages at *institution 2*. Across all teaching methodologies, the number of participants from each institution remained consistent, with 6 from *institution 1* and 14 from *institution 2* in the tutoring group, 7 from *institution 1* and 16 from *institution 2* in the GBL group, and 7 from *institution 1* and 15 from *institution 2* in the CBL group. The results for the students' performance on multiple-choice questions before and after the lecture followed by peer tutoring, GBL, or case study are shown in Fig. 1. The number of correct answers before the didactic activities did not differ among groups because of group distribution (mean/SD: peer tutoring = 2.071 ± 1.072; GBL = 1.938 ± 1.237; CBL= 2.263 ± 1.147) based on pretest performance ($P = 0.709$). After the lecture and the additional teaching strategies were implemented, the distribution of scores (means ± SD) was as follows: peer tutoring = 2,786 ± 1,369; GBL = 3,188 ± 1,682; CBL = 3.118 ± 1.495. Only the GBL group demonstrated a significant increase in the number of correct answers compared with the baseline ($P = 0.003$). However, there was no significant difference in comparison to the other strategies at the same time.

Regarding the assessment of anxiety, there was no difference among groups for both trait and state anxiety (Fig. 2) regardless of the moment evaluated or the complementary teaching methodology applied. The scores for both trait and state anxiety were, on average, >40, indicating a moderate degree of anxiety in the students.

Regarding the individual study strategies reported by the veterinary medicine students, there was no significant

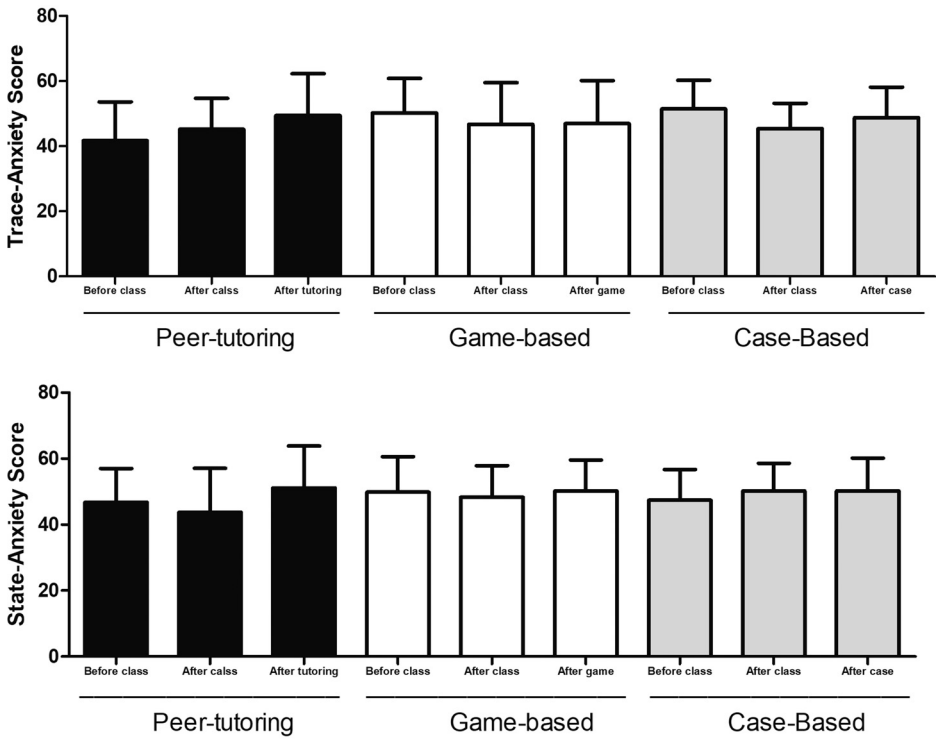
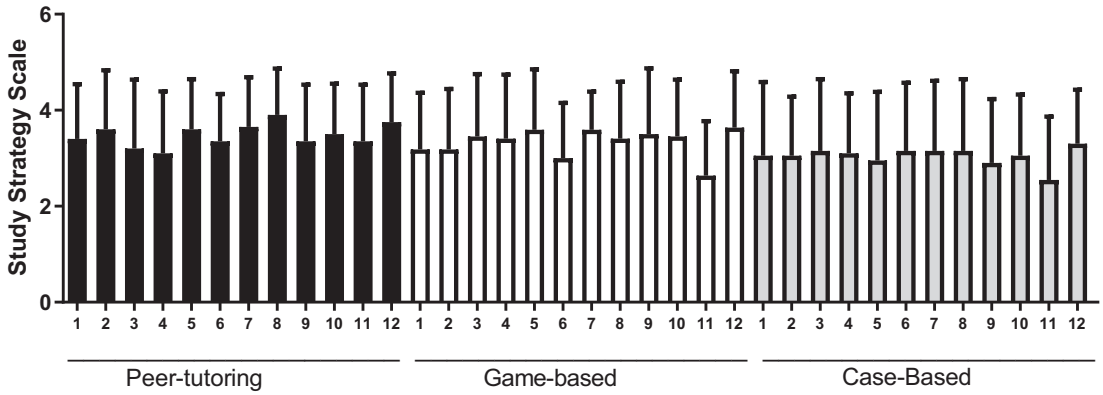


Figure 2. Trait anxiety (*top*) and state anxiety (*bottom*) scores [State-Trait Anxiety Inventory (STAI)] presented by veterinary medicine students who received didactic activities involving traditional lectures in addition to peer tutoring, game-based learning, or case-based learning. Friedman test at 5% significance between different times in the same group; Kruskal–Wallis test at 5% significance between different groups at the same time point.



1. I try to identify the ideas when the teacher is teaching.
2. I learn new words or ideas by imagining a situation in which they appear.
3. I rewrite what I am reading in my own words.
4. I often stop while reading and review or think about what I have read.
5. When studying a subject in this course, I try to relate ideas in a way that makes sense.
6. I try to make sure that I am understanding what the professor teaches during the class in this subject.
7. I try to find connections between what I am learning and what I already know.
8. I try to find connections between what I am studying and my own experience.
9. When I read, I use the chapter headings as a guide to find the main ideas.
10. I try to see how what I am studying can be applied in my daily life.
11. When I review the content of classes in this discipline, I also review the activities carried out outside the classroom about the subject.
12. I try to make connections between the various ideas of the subject I am studying.

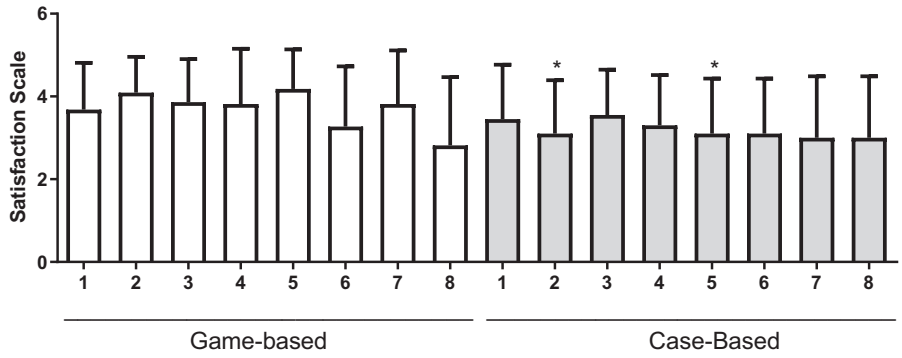
Figure 3. Frequency with which students of veterinary medicine who received didactic activities involving traditional lectures associated with peer tutoring, game-based learning, or case-based learning performed autonomous study activities. The questionnaire was adapted from Ref. 23. Kruskal–Wallis test at the 5% significance level.

difference for any item, indicating that the students presented similar patterns in choosing the way they studied (Fig. 3). Comparison of the perceptions and opinions of students who participated in active methodologies (GBL and CBL) showed that the students believed that GBL promoted greater stimulation of self-study (mean/SD = 4.091 ± 0.867) and problem-solving skills (mean/SD= 4.182 ± 0.958) (P = 0.010) and contributed to the understanding of group dynamics (P = 0.007) compared with CBL (mean/SD = 3.100 ± 1.294 and 3.100 ± 1.334) (Fig. 4).

DISCUSSION

The present study observed benefits in the academic performance of veterinary medicine students who used GBL in the study of endocrine physiology compared with peer tutoring and CBL as supplementary strategies to expository dialogue classes. GBL promoted greater stimulation of self-study and problem-solving skills and contributed to the development of group interaction compared with the group who received CBL. None of the strategies changed anxiety levels. Studies that compare different active teaching methodologies as supplementary methods in the study of endocrine physiology among students of veterinary medicine are scarce. Previous studies have demonstrated the benefits of active methodologies in the study of the physiology of other systems for students from different courses (5, 18, 27), with reports of greater engagement, participation, and learning, which enable the maximization of the teaching/learning process to prepare more qualified professionals (28). The implementation of active learning methodologies, such as game-based learning (GBL) and case-based learning (CBL), is believed to significantly enhance students' attitudes toward their learning experiences by promoting engagement, interactivity, and problem solving. These methodologies not only foster a deeper understanding of the subject matter but also create a positive and motivating learning environment. Additionally, these methodologies encourage students to take ownership of their learning process, leading to increased satisfaction and self-efficacy. This shift in attitudes is crucial for promoting a more constructive and effective learning journey (29–32). However, in the present study these effects were not as pronounced (no significant difference), probably because of the comparison of active methodologies (GBL and CBL) in relation to a control group who received peer tutoring.

Many studies have compared groups that use active methodologies and control groups with no additional strategy (33–35). In the present study, peer tutoring was used as a "placebo" tool to provide additional exposure to the content at the same time in all groups since the observed effects could be generated (and masked) by simply increasing the amount of contact with the content and not by the teaching strategies themselves. Peer tutoring is a widely used teaching method that involves directing and removing doubts from students in pairs at more advanced levels. This approach is already approved in the discipline. It enables the creation of links associated with the strengthening and review of content and helps students to better retain knowledge (36). Studies that have evaluated the effect of peer tutoring have observed significant improvements in learning with greater



*significantly different for the same statement in the other group

1. The active methodology is a better method of teaching and learning than the conventional lectures.
2. Active methodology promotes students' self-study and problem-solving skills.
3. The active methodology helped in better knowledge retention.
4. The active methodology helped to improve students' communication skills.
5. The active methodology helped to understand the principles of group dynamics.
6. The active methodology deprived students of an opportunity to acquire knowledge from good and experienced teachers.
7. The active methodology facilitates a better and healthier relationship between teacher and student.
8. The active methodology is not an adequate way to learn, being a boring method.

Figure 4. Level of satisfaction of students of veterinary medicine who received didactic activities involving traditional lectures associated with peer tutoring, game-based learning, or case-based learning. Questionnaire adapted from Refs. 2, 21, 22. Mann–Whitney test at 5% significance.

retention of knowledge and improved academic performance because this method reinforces learning (37, 38). In the present study, similar behavior was observed between peer tutoring and the active methodologies used. It has previously been reported that peer tutoring can enable more learning during sessions (39). However, depending on the affective involvement between tutors and students, there may be behaviors of boredom and frustration, making the performance neutral (39).

The best result observed for GBL in the present study can be attributed to the ludic effect of the use of games with educational purposes (40). Several studies have reported the benefits of this strategy, which allows students to fix and memorize the content dynamically, leading to greater interaction and centralization of learning for students (41–45). Such reports were confirmed in the present study, including students' reports on the satisfaction assessment. GBL is highly preferred among students because of its approach, which allows for greater dynamics, communication, and interaction between participants and enables more dialogue for problem solving (46–48). According to previous studies, GBL also facilitates better self-study, synchronization of learning with skill development, and problem-solving capacity (49, 50), corroborating the present results. Thus, GBL emerges as a promising alternative to improve student engagement and motivation while improving students' interest and performance (51).

In our study, CBL showed lower satisfaction reports by the participants than GBL. The use of this methodology is very common in courses in the health area, such as nursing (52), physiotherapy (53), medicine (54), and even veterinary medicine (55, 56). However, it is speculated that the use of clinical cases requires more bibliographical research work and discussion with peers that may be performed in a succinct and superficial way (54) despite the use of simulations of clinical situations that support interaction, engagement, and understanding of the content (57). CBL requires more communication between students to discuss the case (58), and when this is not done properly students may segregate and divide tasks with a decrease in engagement (59).

Overall, in the present study the methodologies used provided a very low and similar effect on the baseline level of knowledge at follow-up. Regardless of the chosen methodology, the participation and dedication of students is essential. Most students have spent most of their academic lives in passive learning environments, and the challenge is to help students understand the need to become active peers in learning (60). Thus, we can highlight the importance of previous training for students to enable better results and improve the teaching/learning process (57, 61). The success of active methodologies depends on students' previous experience and the type of methodology used (62, 63).

In the present study, we did not observe a significant change in the students' anxiety level regardless of the methodology used and the time of assessment of this parameter. However, it was observed that, on average, the evaluated students had moderate levels of anxiety. Anxiety is associated with an emotional state of excessive concern about a particular subject. It generates deficits in concentration and adaptation to the environment (64). The identification and minimization of anxiety in students is a fundamental factor considering the existence of stressors in the university environment that can compromise the teaching/learning process (65, 66) because of excessive daily demands for performance, learning, responsibility, and frustrations (67). The teaching methodology used has a strong impact on students' anxiety and can minimize or enhance the intensity of this condition (68, 69). It has been reported that active teaching methodologies can be advantageous for reducing anxiety because they provide a relaxed environment, better interaction, and increased motivation (70). However, for students who already have a certain degree of anxiety, negative effects may occur because of the need for forced interaction or the inability to respond and participate in front of peers (71, 72). In the present study, the active methodologies were applied as supplementary to the traditional techniques, so the increase in

the amount of school activities may play an important role that should be further explored by future studies.

Regarding the learning strategies used by students to understand and study endocrine physiology, no significant differences were observed between the different methodologies. Regardless of the teaching methodology used, the students maintained their behavior in the individual studies. Students who use diversified learning strategies to assimilate the content of a course tend to perform better. The analysis of students' behavior may therefore be a confounding factor of performance (73), and its evaluation was included in the present study. Among the main strategies used, the preparation of summaries about the subject, conducting practices related to the study, and association of the content taught with knowledge and students' own experiences are notable. Such measures are essential for complementing academic results (74) because the introduction of active methodologies did not encourage improvement or a change of habits in the evaluated sample.

Our findings demonstrate very similar results for the supplementary use of peer tutoring, GBL, and CBL, with a slight advantage for GBL due to the greater stimulus for self-study and problem-solving ability as well as the development of group interaction. The need to prepare students for the application of active methodologies is emphasized since the success of such methodologies depends on the degree of commitment to the development of activities. Additionally, the game used for GBL in the present study was developed by the authors and is an unprecedented tool that can prove useful for improving knowledge retention in students of veterinary medicine. This can be considered one of the strong points of our study, since this game can be adapted for application to students of other courses that include endocrine physiology as a curricular component.

DATA AVAILABILITY

Data will be made available upon reasonable request.

SUPPLEMENTAL INFORMATION

Supplemental Table S1: https://doi.org/10.6084/m9.figshare.24431467.

Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.24431473.

Supplemental Fig. S2: https://doi.org/10.6084/m9.figshare.24431479.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Centro Universitário do Cerrado Patrocínio (UNICERP) and Centro Universitário de Lavras (UNILAVRAS) for data collection.

GRANTS

FAPEMIG (Research Support Foundation of Minas Gerais), CAPES (Coordination for the Improvement of Higher Education Personnel), and CNPq (National Council for Research and Development) provided financial support.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

E.F.A. and L.J.P. conceived and designed research; M.V.R.A. and R.B.L. performed experiments; M.V.R.A., E.F.A., and L.J.P. analyzed data; M.V.R.A., R.B.L., E.F.A., and L.J.P. interpreted results of experiments; M.V.R.A., R.B.L., E.F.A., and L.J.P. prepared figures; M.V.R.A., R.B.L., E.F.A., and L.J.P. drafted manuscript; M.V.R.A., R.B.L., E.F.A., and L.J.P. edited and revised manuscript; M.V.R.A., R.B.L., E.F.A., and L.J.P. approved final version of manuscript.

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