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Original Article

Effects of co-administration of borneol and ketamine on anesthesia parameters in male rats

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ABSTRACT

Introduction: The side-effects and short anesthesia caused by ketamine limit its individual application. Moreover, the anti-inflammatory, sedative and muscle relaxant effects of borneol as an analgesic and anesthetic have promoted its application in Chinese and Japanese medicine. This study examined the effects of co-administration of borneol and ketamine on anesthesia parameters in male rats.

Methods: Twenty-four male rats were divided into four groups, and respectively received borneol (Bo), ketamine (K), borneol-ketamine (BoK) and diazepam-ketamine (DK). Parameters recorded included the heart rate, respiratory rate, body temperature and pain reflexes (ear, tail and pedal), induction time, duration of surgical anesthesia and walking time.

Results: Borneol did not individually induce surgical anesthesia, which was reached faster in group DK than in group BoK. Insignificant differences in duration of surgical anesthesia, walking time and pain reflexes were observed between groups BoK and DK. The heart rate, respiratory rate and body temperature were higher in group BoK than in group DK.

Conclusion: The pre-anesthetic and hypnotic effects of borneol were similar to those of diazepam. Further studies are, however, required for determining the exact pharmacological mechanism of borneol.

Keywords:
Borneol
Monoterpenes
Injectable anesthesia
Gamma-aminobutyric acid (GABA)
Rat

Introduction

Surgical procedures require low-risk and reliable injectable anesthetics. Despite the higher safety of inhalation anesthetics than that of injectable agents, their use is limited by their side-effects, scarcity, high cost and risk for operating room technicians. Injectable anesthetics used in animals include ketamine and thiopental (Furtado and Andrade, 2013). As a phencyclidine derivative, an N-methyl-aspartate receptor antagonist and adjuvant for local anesthesia, ketamine induces general and dissociative anesthesia in animals and human (Kurdi et al., 2014; Flecknell, 2016; DeRossi et al., 2009; Othman et al., 2016); nonetheless, the short anesthesia, seizure and psychotropic side-effects such as delirium and recurrent

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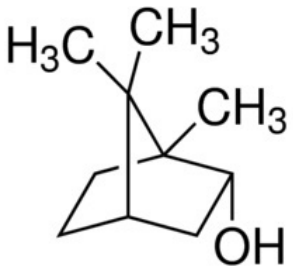

FIGURE 1. Chemical structure of (1S) - (-) - borneol

hallucinations caused by ketamine and its lack of muscle relaxant effects restrict its individual usage (Gao et al., 2016; Zanos et al., 2018).

Ketamine is therefore used in combination with medications such as benzodiazepines, e.g. diazepam, and α2-receptor agonists, e.g. xylazine (Gao et al., 2016; Adel et al, 2017). In addition to conventional synthetic drugs, natural extracts, essential oils and active herbal components are used as a pre-anesthetic and alternative to or in combination with ketamine. The side-effects of medicinal plants are fewer and more tolerable than those of synthetic agents (Karimi et al., 2015). The sedative-hypnotic and pre-anesthetic properties of herbal extracts and essential oils such as *Rosa damascena*, *Humulus lupulus*, *Viola odorata* L., *Cannabis sativa* and *Myrtus communis* (Abbasi Maleki et al., 2012; Shishehgar et al., 2012a, Shishehgar et al., 2012b; Monadi and Rezaei, 2013; Rezaei et al., 2014; Yousefi et al., 2018) and herbal active components such as thymol and eugenol were reported in literature (Tsuchiya, 2017).

As a bicyclic monoterpene in Chinese and Japanese medicine for pain relief and anesthesia (Figure 1) (Hattori, 2000), borneol is found in the essential oils of herbs such as *Valerina officinalis* and *Lavender officinalis*. The pharmacological features of borneol studies reported include anesthetic, analgesic and anti-inflammatory properties (Hattori, 2000; Almeida et al., 2013; Ji et al., 2020). Research suggests the co-administration of borneol and propofol prolongs anesthesia (Lin et al., 2006). Given the properties of borneol and lack of relevant studies, the present research was conducted to investigate the effects of the co-administration of borneol and ketamine on anesthesia parameters in male rats.

Material and methods

Drugs

We used (1S) - (-)- borneol crystal (Merck, Germany), ketamine hydrochloride (Alfasan, the Netherlands) and diazepam hydrochloride (Darupakhsh, Iran). Borneol was diluted and dissolved in a solution of dimethyl sulphoxide in deionized water (0.5% v/v).

Animals

This experimental study was conducted in Islamic Azad University of Urmia, Iran in 2020 recruiting 24 male Wistar rats (Urmia, Iran) weighing 190-220g. The animals were provided with free access to food and water except during the test and maintained in standard laboratory conditions, i.e. 23±1°C and 12h light-dark cycle. The present study was approved by the Ethics Committee of Islamic Azad University of Urmia (IR.IAU.URMIA.REC.1399.026).

Groups and experimental design

According to a pilot study conducted in our laboratory, the animals were randomly assigned to four groups of six as follows: 1- Bo receiving only 500mg/kg of borneol; 2- K receiving only 75mg/kg of ketamine; BoK receiving 500mg/kg of borneol and 1min before receiving 75mg/kg of ketamine; 4- DK receiving 2.5mg/kg of diazepam, 1min before receiving 75mg/kg of ketamine. All the injections were performed intraperitoneally at 1ml/kg, as recommended in the literature (Abbasi Maleki et al., 2012; Shishehgar et al., 2012a, Shishehgar et al., 2012b; Monadi and Rezaei,2013; Rezaei et al., 2014; Molina et al., 2015).

Anesthesia parameters

After losing their righting reflex, the animals were placed on their back and durations of induction and surgical anesthesia and walking time were recorded using a chronometer (Q&Q, Japan). The respiratory rate was measured using a counter by observing chest movements. An electrocardiogram (CardiTouch, Japan) was

TABLE 1: The effect of Bo, BoK, K, and DK groups on induction time, duration of surgical anesthesia (SA) and, walking time

Reflex Group	Induction time	Duration of SA	Walking time
Bo	-	-	-
K	3.63±0.96	42.28±1.82	45.91±2.61
BoK	3.15±0.23	51.85±0.23**	55.00±0.0**
DK	2.16±0.40**	54.00±2.09**	56.16±1.94**
Sig. (2-tailed)	0.003	0.001	0.001
F	(2,15) = 8.666	(2,15) = 90.141	(2,15) = 53.429

Values are given as mean±SEM (n=6). Data were analyzed by one-way ANOVA and Tukey's complementary test. **P<0.01 as compared to the ketamine group. Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

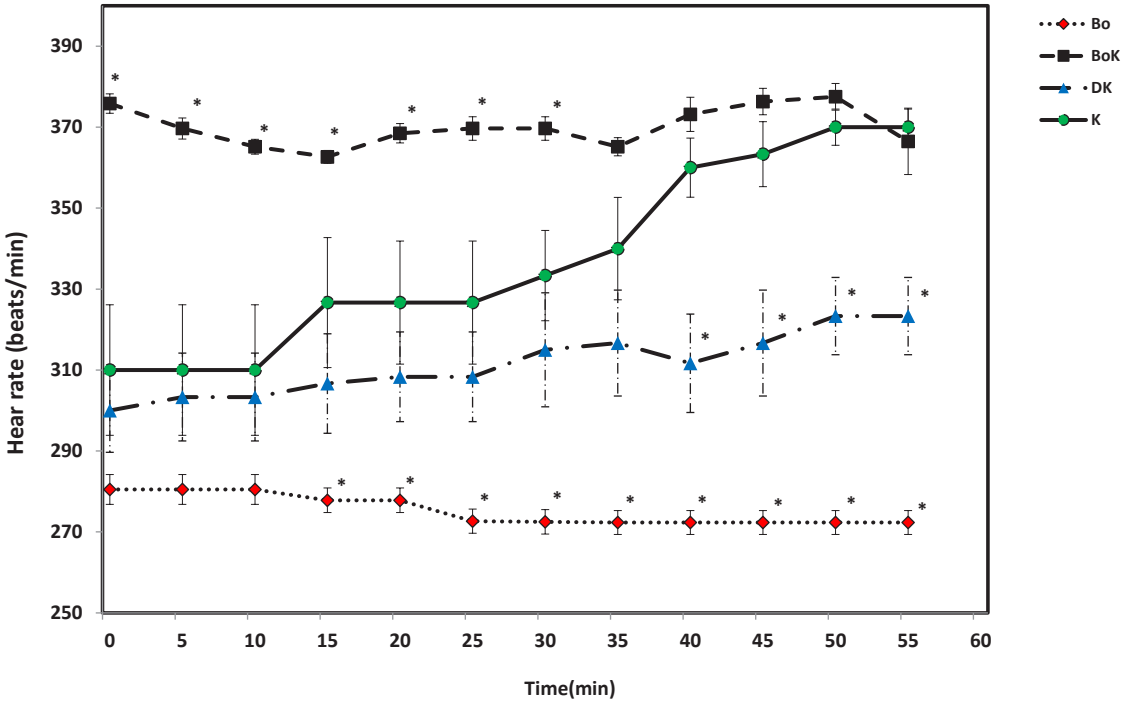

FIGURE 2. The effect of Bo, K, BoK, and DK groups on heart rate. Values are given as mean±SEM (n=6). Data were analyzed by one-way repeated measures ANOVA. *P<0.05 as compared to ketamine group. Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

used at 50mm/s to record the heart rate for 55min every 5min until the righting reflex was restored. The body temperature was also recorded using a digital thermometer inserted at least 3mm into the animal's rectum. The animals were placed on an electric heating pad to prevent their hypothermia-induced death during anesthesia.

From loss of the righting reflex to restoring the reflexes, depth of anesthesia was controlled and recorded by evaluating every 5min the withdrawal reflexes, involving the ear, tail and pedal, and through pinching the ear using plastic forceps, the web between the toes of the hind limb and the distal part of the tail (the thumb and index finger). A person blinded to grouping recorded all the reflexes (Hajighahramani and Vesal, 2007) on a scale of 0-3 defined as 0: no reflex, 1: low intensity reflex, 2: moderate intensity reflex and 3: high intensity reflex.

Statistical analysis

The data were analyzed using SPSS 21 at a significance level of P<0.05, diagrams were plotted in Excel 2019 and expressed as mean±SEM. One-way repeated-measures ANOVA was used to investigate the combined effect of treatment and duration of anesthesia on the heart rate, respiratory rate and body temperature

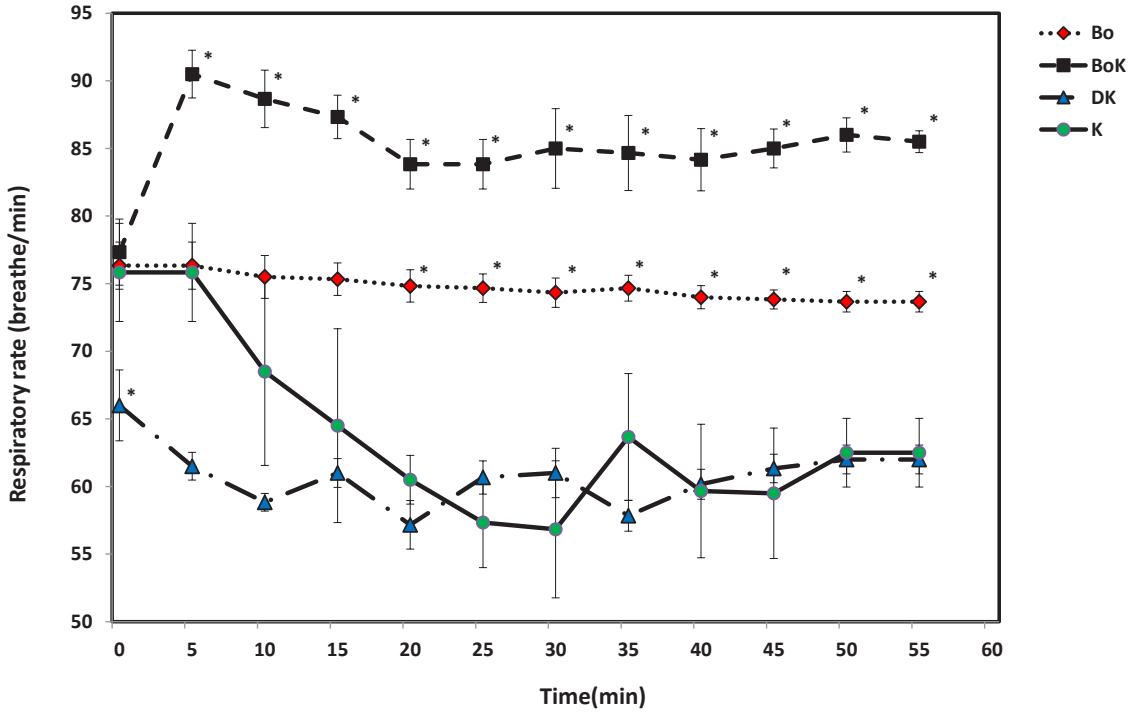

FIGURE 3. The effect of Bo, K, BoK, and DK groups on respiratory rate. Values are given as mean±SEM (n=6). Data were analyzed by one-way repeated measures ANOVA. *P<0.05 as compared to ketamine group. Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

during anesthesia. One-way ANOVA and complementary Tukey's test were performed to compare the duration of anesthesia. The Kruskal-Wallis and Mann-Whitney U tests were also used to analyze the pain data.

Results

Effects of borneol, ketamine, borneol-ketamine and diazepam-ketamine on durations of induction and surgical anesthesia and recovery time

Surgical anesthesia was not induced in group Bo; nevertheless, it was induced in group DK (2.16±0.40) faster than in groups BoK (3.15±0.23, P<0.05) and K (3.63±0.96, P<0.05). Insignificant differences were observed between groups BoK (51.85±0.23) and DK (54.00±2.09) in terms of duration of surgical anesthesia (P>0.05), which was shorter in group K (42.28±1.82) than in the other two groups (P<0.05). Group BoK (55.00±0.0) was insignificantly different from group DK (56.16±1.94) in terms of walking time (P>0.05). Shorter surgical anesthesia in group K (45.91±2.61) caused recovery to begin earlier than in groups BoK and DK (P<0.05, Table 1).

Effects of borneol, ketamine, borneol-ketamine and diazepam-ketamine on the heart rate

Factorial ANOVA showed significant differences in the mean heart rate during anesthesia [partial η2=0.40, F(11, 220)=13.55, P=0.001]. Significant interactions between the treatments and time [partial η2=0.57, F(33, 220)= 8.94, P=0.001] significantly increased the heart rate during anesthesia in group BoK and significantly decreased it in group Bo than in the other treatment groups. The mean heart rate was higher in group BoK than in group DK (P<0.05). A significantly higher heart rate was recorded in group K compared to in group DK from 40min into the test until its end (P<0.05). Similarly, the mean heart rate was higher in group K than in group Bo from 15min into the test until its end (P<0.05). The heart rate in group BoK was, however, higher than that of group K up to minute 30 of the test (P<0.05, Figure 2).

Effects of borneol, ketamine, borneol-ketamine and diazepam-ketamine on the respiratory rate

Factorial ANOVA showed significant differences in the mean respiratory rate during anesthesia [partial η2=0.20, F(11, 220)= 5.07, P=0.004]. Significant interactions between the treatment and time [partial η2=0.34, F(33, 220)= 3.42, P=0.002] significantly increased the respiratory rate during anesthesia in group BoK and sig-

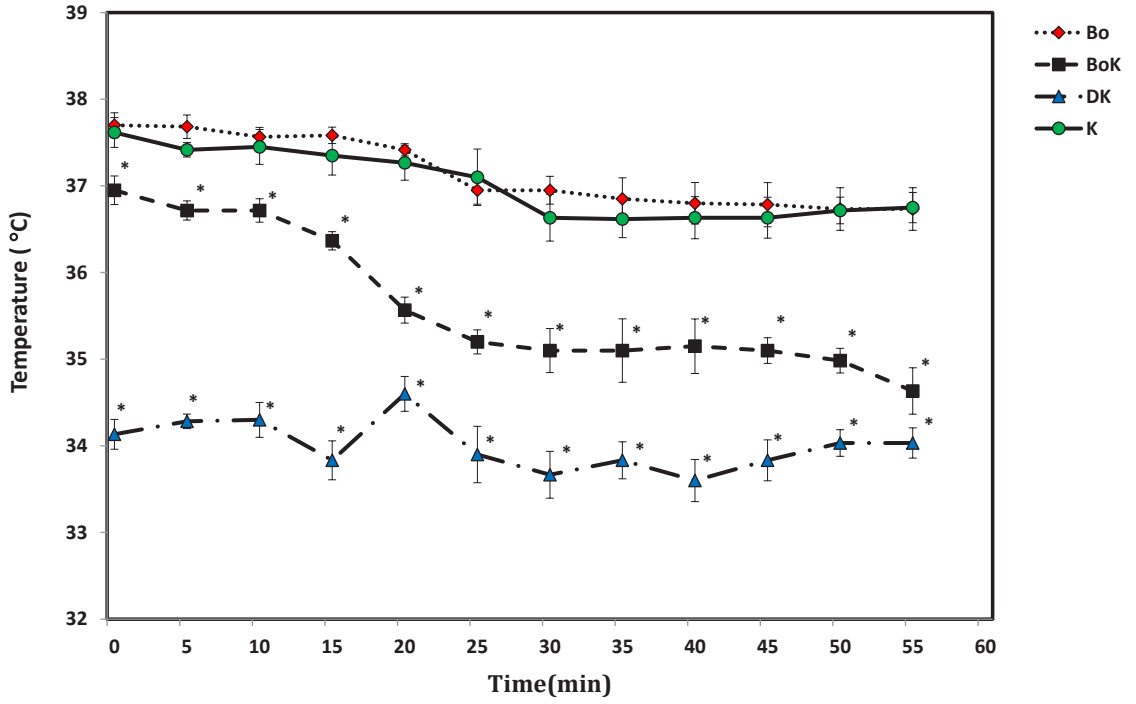

FIGURE 4. The effect of Bo, K, BoK, and DK groups on body temperature. Values are given as mean±SEM (n=6). Data were analyzed by one-way repeated measures ANOVA. *P<0.05 as compared to ketamine group. Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

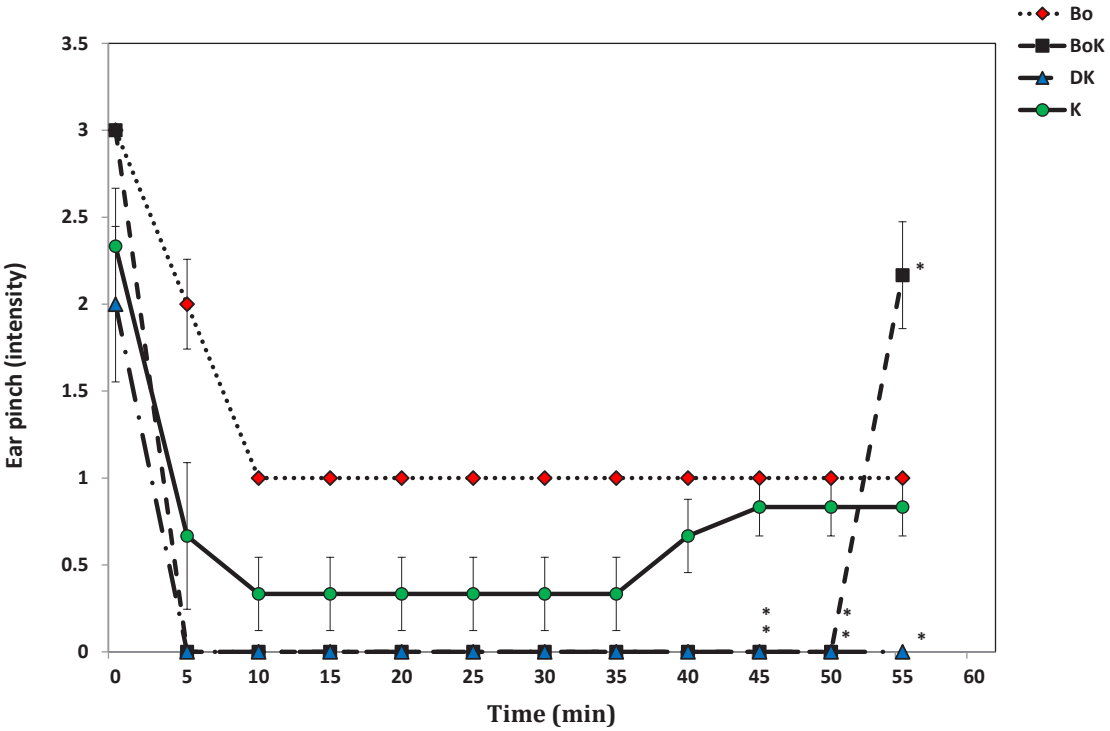

FIGURE 5. The effect of Bo, K, BoK, and DK groups on ear reflex. Values are given as mean±SEM (n=6). Data were analyzed by Kruskal-Wallis and Mann-Whitney U tests. *P<0.05 as compared to ketamine group. Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

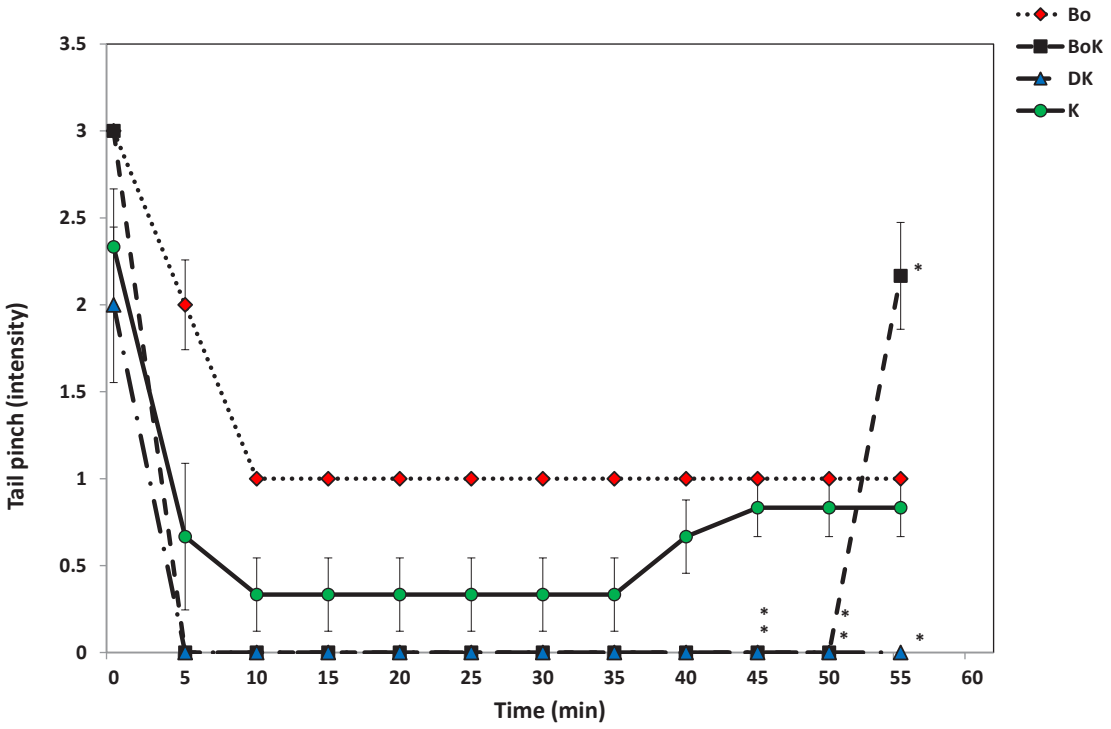

FIGURE 6. The effect of Bo, K, BoK, and DK groups on tail reflex. Values are given as mean±SEM (n=6). Data were analyzed by Kruskal-Wallis and Mann-Whitney U tests. $^{*}P<0.05$ as compared to ketamine group.
Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

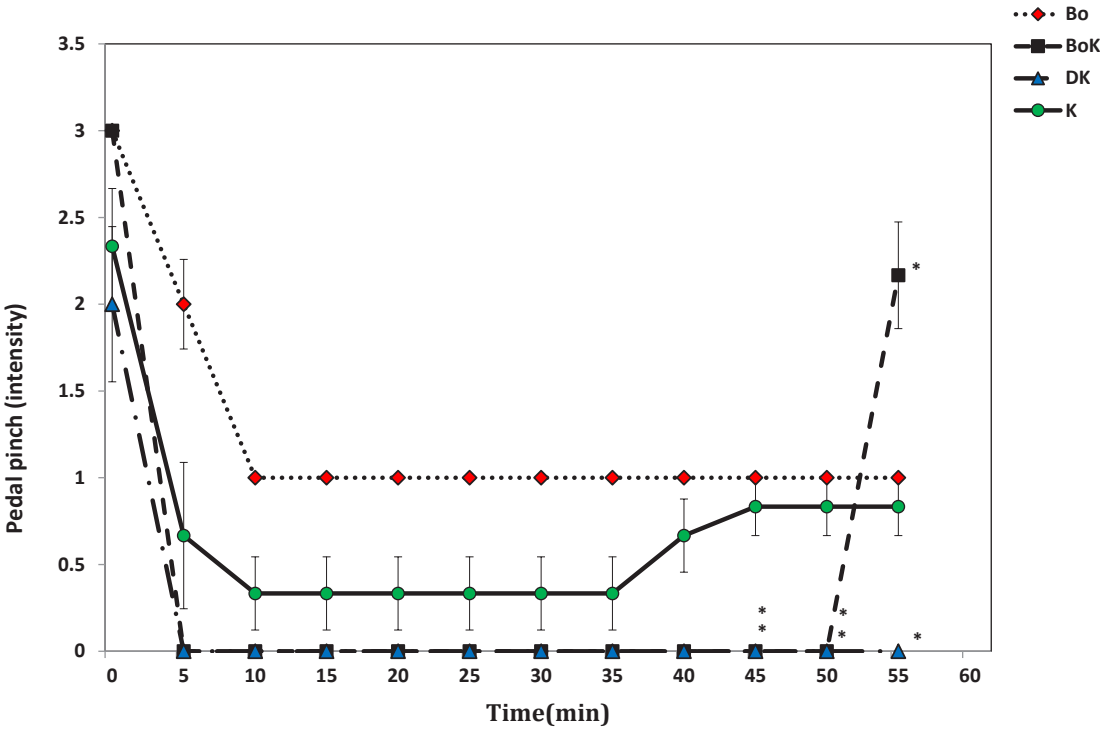

FIGURE 7. The effect of Bo, K, BoK, and DK groups on tail reflex. Values are given as mean±SEM (n=6). Data were analyzed by Kruskal-Wallis and Mann-Whitney U tests. $^{*}P<0.05$ as compared to ketamine group.
Bo: Borneol; BoK: Borneol-ketamine; K: ketamine; DK: Diazepam-Ketamine.

nificantly lowered it in groups K and DK than in the other groups. The respiratory rate in group BoK was higher than that in group DK (P<0.05) and in group Bo higher than that in group K from 20min into the test until its end (P<0.05, Figure 3).

Effect of borneol, ketamine, borneol-ketamine and diazepam-ketamine on the body temperature

Factorial ANOVA showed significant differences in the mean body temperature during anesthesia [partial η2=0.55, F(11, 220)= 24.53, P=0.001). Significant interactions between the treatment and time [partial η2=0.32, F(33, 220)= 3.18, P=0.002) significantly increased the mean body temperature during anesthesia in groups Bo and K and significantly reduced it in group DK compared to in the other groups. Although the body temperature was lower in group DK than that in group BoK (P<0.05), groups Bo and K were insignificantly different in this regard (P>0.05) (Figure 4).

Effects of borneol, ketamine, borneol-ketamine and diazepam-ketamine on the ear, tail and pedal reflexes

No significant differences were observed between groups BoK and DK in terms of the inhibition of ear, tail and pedal reflexes (P>0.05, Figures 5-7, respectively). These reflexes were, however, more effectively inhibited in group K than in group Bo from 45 to 55 min into the test (P<0.05).

Discussion

The present findings demonstrated the sedative and hypnotic effects of borneol on rats; nevertheless, this compound did not individually induce surgical anesthesia, which can be explained by its dose and low solubility. Muscle relaxation and sedative effects of borneol were also reported in literature (Buchbauer et al., 1992; Santos et al., 2019). The sedative and hypnotic properties of medicinal plants can be mainly attributed to gamma-aminobutyric acid (GABA) as an inhibitory neurotransmitter (Bruni et al., 2021). The $GABA_A$ and $GABA_C$ receptors exert their effects by allowing the passage of chloride ions into cells (Mennini et al., 1993; Mihic and Harris, 1997; Enz and Cutting, 1998). Stimulation of the $GABA_A$ receptor by its modulators such as benzodiazepines and barbiturates cause anti-anxiety, sedative-hypnotic and anesthetic effects (Chebib and Johnston, 2000; Goetz et al., 2007; Garcia et al., 2010).

Significant effects of borneol on GABA receptors ($a_1b_2g_{2L}$) were reported in literature. The weak effect of borneol on the GABA concentration is equivalent to that of etomidate and stronger than that of diazepam (Granger et al., 2005). Research also suggests the sedative-hypnotic and anesthetic effects of different monoterpenes (Bianchini et al., 2017; Tsuchiya, 2017). Furthermore, the effect of propofol was promoted three times in combination with herbal monoterpenes, including borneol, carveol, menthol and trans-sobreol. These monoterpenes prolong the propofol-induced anesthesia by inhibiting its metabolism, which is consistent with the present results, suggesting the similarity of borneol and diazepam in terms of their properties (Lin et al., 2006). These results also confirm the anesthetic properties of herbal monoterpenes such as borneol.

The side-effects of anesthetics mainly include suppressing the cardiovascular system in animals. High doses of anesthetics can be associated with cardiovascular disorders and cardiac arrest. Minimizing the suppressive effect of anesthetics on the cardiovascular system is therefore crucial (Vesal, 2004; Grimm et al., 2015). In line with the present findings, ketamine alone was found to increase the heart rate and blood pressure (Toso et al., 1992; Zanos et al., 2018). The present research reported a higher heart rate in group BoK than in group DK, which suggests the minimum suppressive effect of borneol on the cardiovascular system. Similarly, monoterpenes such as borneol were found to help prevent and treat cardiovascular diseases. The beneficial effects of the combined use of monoterpenes and ketamine were therefore confirmed (Santos et al., 2011). In addition to these effects, respiratory system suppression by anesthetics causes hypoxia, elevated concentration of carbon dioxide and cardiac arrest in animals (Vesal, 2004; Grimm et al., 2015). The present findings showed the more promising results of the co-administration of borneol and ketamine than those of diazepam-ketamine in terms of respiratory suppression.

As a side-effect of anesthetics and a cause of animal mortality, hypothermia should be prevented and the body temperature controlled through its monitoring during surgical procedures (Vesal, 2004; Grimm et al., 2015). The present study found the benefits of borneol and its co-administration to include increasing the body temperature compared to diazepam-ketamine.

Surgeons pinch end limbs such as the ear, tail and ped-

al to find the depth of anesthesia and ensure the sedation adequacy during surgeries (Hedenqvist et al., 2000; Hajighahramani and Vesal, 2007). In case of an inadequate depth of anesthesia, pinching these limbs increases the respiratory rate or causes the animal to moan or move these parts (Hedenqvist et al., 2000; Hajighahramani and Vesal, 2007). The present findings showed the poor control of these reflexes in group Bo compared to in the other three groups. The comparable control of reflexes performed in groups BoK and DK suggested the adequate analgesic effect and anesthetic depth caused by borneol combined with ketamine. In line with the present results, the analgesic and anti-inflammatory properties of borneol were reported in the literature (Almeida et al., 2013). The significant analgesic and anti-inflammatory effects of borneol on animals were also reported in the models of pain such as formalin, hot plate and writhing tests as well as inflammation induced by carrageenan. Borneol inhibits acute and chronic phases of formalin (Almeida et al., 2013). The inadequate analgesic effects of ketamine can therefore be compensated through its co-administration with borneol during anesthesia.

Despite the poorly-known mechanism of anesthetics, borneol was found to exert pre-anesthetic effects through GABAergic pathways, as with diazepam. The strengths of the present research included pioneering the determination of the pre-anesthetic effects of borneol and its weaknesses included failure to determine the exact pharmacological mechanism of borneol.

Conclusion

Borneol creates fairly good sedation and pre-anesthesia if co-administered with ketamine despite the poor anesthetic properties of borneol alone and given its similar properties to those of diazepam. Borneol can therefore be co-administered with standard medications such as ketamine to induce pre-anesthesia in rodents. Determining the exact pharmacological mechanism of borneol requires further studies.

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Conflicts of interest

The authors declared no conflicts of interest regarding the publication of the present article.

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