Original Article

The Effect of Royal Jelly on the Level of Consciousness in Patients with Traumatic Brain Injury: A Double-Blind Randomized Clinical Trial

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ABSTRACT

Background: Patients with traumatic brain injury (TBI) experience changes in their level of consciousness (LOC). Royal Jelly is used in the treatment of neurological diseases. **Objective:** This study aimed to examine the effect of royal jelly on the LOC of patients with TBI. **Methods:** This double-blind randomized trial was performed in 2020 on 61 patients with TBI admitted to the intensive care unit. The patients were recruited consecutively and randomly assigned to an intervention (n = 33) and a control (n = 28) group. Patients in the intervention group received 3000 mg of royal jelly orally each day for 14 days, while those in the control group received routine care. The LOC was evaluated using the Glasgow Coma Scale (GCS) and Full Outline of Unresponsiveness (FOUR) score from day 1 to day 14. Data were analyzed using the repeated measures analysis and analysis of covariance. **Results:** The mean baseline GCS scores of the intervention and the control group were 4.39 ± 0.61and 4.82 ± 0.77, respectively, and changed to 11.93 ± 2.41 and 7.60 ± 2.51 at the end of the 14th day (P < 0.001). Furthermore, the mean baseline FOUR scores of the intervention and the control groups were 6.06±0.93 and 6.42 ± 1.16, respectively, and changed to 13.88 ± 2.57 and 9.71 ± 2.40 at the end of the study (P < 0.001). **Conclusion:** Using royal jelly for 2 weeks could improve the LOC of patients with TBI. However, further studies are recommended to determine the dose and duration of the usage.

KEYWORDS: *Critical care unit, Level of consciousness, Royal jelly, Traumatic brain injury*

INTRODUCTION

Most patients with traumatic brain injury (TBI) experience changes in their level of consciousness (LOC).[1] There is currently no definitive treatment to prevent the progress of brain damage and raise the LOC in patients with TBI.[2] Drugs used in traditional medicine are primarily obtained from natural products.[3] Royal jelly is a natural product of the honeybee with multiple uses in medicine.[4,5] Royal jelly has antioxidant, cholesterol-lowering, anti-inflammatory, anti-hypertensive, anti-tumor, antimicrobial, anti-diabetic, memory improvement, and immune function enhancement properties.[4-7]

One of the unique ingredients of royal jelly is 10-hydroxy-2-decanoic acid (10HDA), with strong antioxidant effects. Another ingredient in royal jelly is adenosine monophosphate N1 oxide (AMP. N1 Oxide), which considerably affects the central nervous system and increases the proliferation of neural stem cells.[8] A study has shown neurogenesis properties of royal jelly and its role in neuronal differentiation.[4] This natural product also increases oxygen delivery to brain tissue, and consequently, improves memory and cognition processes.[9] Another study also showed the promising effects of royal jelly in treating cognitive impairment in

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Submitted: 26-Sep-2021 **Revised:** 29-Jan-2022 **Accepted:** 08-Feb-2022
Published: 29-Jul-2022

How to cite this article: Shafiee Z, Hanifi N, Rashtchi V. The effect of royal jelly on the level of consciousness in patients with traumatic brain injury: A double-blind randomized clinical trial. Nurs Midwifery Stud 2022;11:96-102.

Access this article online

Quick Response Code:

Website: www.nmsjournal.com

DOI: 10.4103/nms.nms_103_21

old age and the early stages of Alzheimer's disease.[10] A review study also reported that the use of royal jelly was effective in the treatment of Parkinson's disease.[11] However, few studies are available on the effects of royal jelly on the LOC in patients with TBI. Considering the favorable effects of royal jelly on neural functions, there is still the question of whether using royal jelly can improve the LOC in patients with TBI.

Objectives

This study examined the effect of royal jelly on the LOC in patients with TBI.

Methods

Study design and participants

This parallel-group double-blind randomized trial was conducted from June 21, 2020, to January 19, 2021, on patients with TBI who were admitted to the intensive care unit (ICU) of Ayat-Allah Mousavi Hospital in Zanjan, Iran. The sample size was estimated based on the results of a pilot study on 15 patients with TBI. In the pilot study, patients received 3000 mg of royal jelly orally each day for 14 days, and their mean FOUR score changed from 11.60 ± 1.51 to 13.10 ± 1.54. Then, considering the test power of 0.90, the confidence level of 0.95, a μ_1 of 10.80, a μ_2 of 13.10, an S_1 of 1.51, and an S_2 of 1.54, and using the formula for the comparison of two means, the sample size for each group was estimated to be 22 patients. However, considering the possible dropouts, we recruited 33 ones in each group.

Inclusion criteria were having a medical diagnosis of TBI, being in the age range of 18–60 years, having a GCS score between 4 and 13, no severe trauma to other organs, not being pregnant (according to the physician's diagnosis and paraclinical studies), no drug addiction, no history of allergic reactions to honeybee products, no history of mental illness or cognitive impairment (based on the patient's relatives report and medical history), no order for being nothing by mouth, and receiving no sedatives through continuous infusion. Exclusion criteria were death, discharge, or transfer from the ICU before the end of the study, a decision to withdraw from the study by the patient, or the patient's legal custodian.

Randomization was done through a block method with quadruple blocks. The letter A was assigned to the intervention group and the letter B to the control group. Six modes, including AABB, BBAA, BABA, ABBA, BAAB, and ABAB, were written in separate sheets. Then, a lottery was held with replacement to allocate participants in the groups by a person outside the research team. Eligible participants were assigned to either of the intervention and control groups based on these sheets. The lottery was repeated 16 times with replacement according to the sample size.

Data collection instruments

The data collection instrument included three forms. The first one consisted of items on the patient's demographics and clinical status, including age, sex, marital status, the score of the Acute Physiology and Chronic Health Evaluation (APACHE II), comorbid diseases, cause of trauma, type of brain injury, brain surgery, receiving mechanical ventilation, and amount of sedative received. APACHE II is a tool used to determine the severity of disease within 24 h of admission to the ICU. The total score of this scale is between 0 and 71. A higher score indicates the severity of the disease and an increased risk of death. The validity and reliability of this tool have been confirmed in Iran.[12]

The second tool was the Glasgow Coma Scale (GCS). This is a valid and reliable scale commonly used for the scoring of LOC and the severity of TBI and its score ranges between 3 and 15. The higher the score, the higher the LOC.[13,14] The third part of the instrument was the Full Outline of Unresponsiveness score (FOUR). FOUR score is a 17-point scale with a score ranging from 0 to 16. A lower FOUR score indicates a worsening LOC. The validity of this scale has already been confirmed.[15] The inter-rater reliability method was used to evaluate the reliability of APACHE II, FOUR score, and GCS. In this way, the LOC and severity of disease of 10 patients were assessed simultaneously by two assessors using these scales, and then the kappa agreement coefficient was calculated at 0.96. The accuracy of the scale used to weigh the royal jelly was checked by weighing a 30-g piece of gold that had previously been weighed accurately.

The APACHE II score was evaluated in the first 24 h of admission of patients to the ICU. In addition to the routine medications, patients in the intervention group received 3000 mg of royal jelly for 14 days. Royal jelly was dissolved in 30 mL of water and administered once a day at noon, through a nasogastric or orogastric tube.[16] Because of surgery, feeding in most patients with TBI begins on the second or 3rd day. Therefore, royal jelly was started from the 3rd day of ICU admission[17,18] and administered by the first author (ZS). Since patients had a low LOC, they were blind to the type of intervention. A research assistant who was blind to the group of patients monitored the LOC of all patients. The LOC was assessed using the GCS and FOUR score from day 1 to day 14. The routine physician visits of all patients were usually performed at 10 a.m., and the last dose of sedative was received at 6 a.m. Therefore, the LOC of all patients was assessed at 10 a.m. (with an interval

of at least 4 h after receiving the last dose of sedative [Figure 1].

Ethical considerations

The ethics approval was received from the Research Ethics Committee of Zanjan University of Medical Sciences (code: IR.ZUMS.REC.1399.058). The study objectives were explained to the patient's custodian and they signed the written informed consent form. They were also assured about the data confidentiality and informed about their right to either participate in or withdraw from the study at any time. The patients' physicians allowed using the royal jelly after examining the contraindications.

Data analysis

Data were analyzed using the SPSS software version 16 (SPSS, Inc., Chicago, Illinois, USA). There was no missing data in this study and the Kolmogorov–Smirnov test showed that the main quantitative data were normally distributed. The Chi-squared and Fisher's exact tests were used to compare the nominal and categorical variables between the two groups. The independent samples *t*-test was used for the between-group comparison of means of quantitative variables such as GCS, FOUR score, APACHE II score, and the duration of mechanical ventilation. Furthermore, repeated measures analysis of variance was used to examine the changes in GCS and FOUR score during the 14 days of the study. Mauchly's test was used to check the assumption of sphericity for both GCS and FOUR score, and the Greenhouse–Geisser test was used for within-subjects comparison. The analysis of covariance (ANCOVA) was used for subgroup analysis of the effect of disease severity on GCS and FOUR score changes at a significance level <0.05. GCS and FOUR score on day 14 were used as dependent variables, group as a fixed variable, and APACHE II score was taken as covariate.

Table 1: Comparison of the demographic variables between the intervention and control groups

Variable	Control, *n* (%)	Intervention, *n* (%)	Fisher's exact test (*P*)
Sex			
Male	33 (100)	26 (92.9)	0.21
Female	0	2 (7.1)	
Marital status			
Single	12 (36.4)	9 (32.1)	0.79
Married	21 (63.6)	19 (67.9)	
History of the disease			
Yes	4 (12.1)	1 (3.6)	0.37
No	29 (87.9)	27 (96.4)	
Cause of trauma			
Driving accidents	30 (90.9)	23 (82.2)	0.35
Fall	3 (9.1)	5 (17.9)	
Type of brain injury			
Subdural hematoma	16 (48.5)	12 (42.9)	0.504
Epidural hematoma	7 (21.2)	4 (14.3)	
Contusion	10 (30.3)	12 (42.9)	
Surgery to drain the hematoma			
Yes	6 (18.2)	3 (10.7)	0.49
No	27 (81.8)	25 (89.3)	

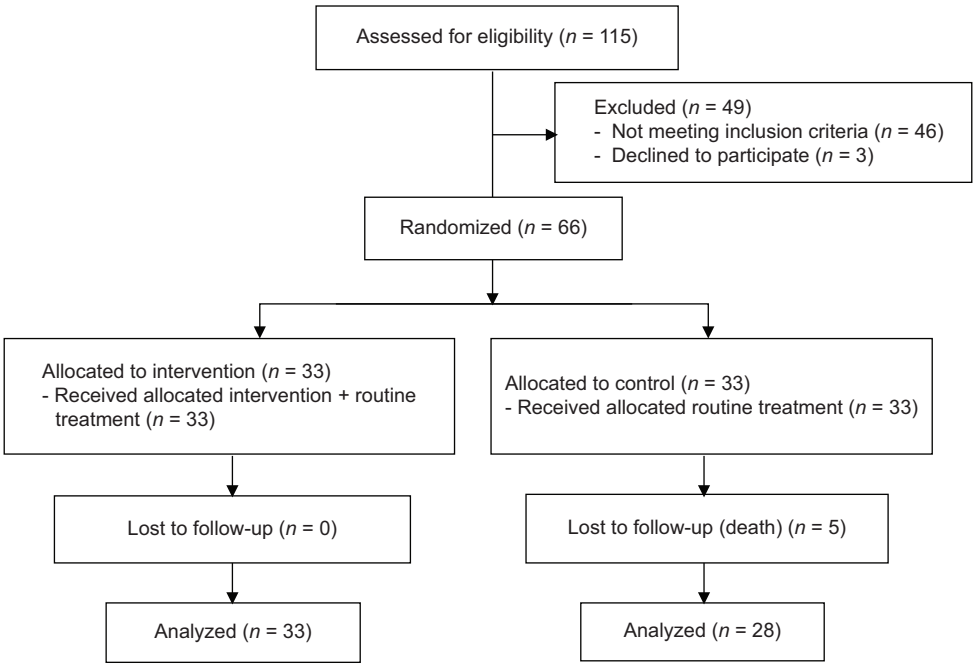

Figure 1: The study flow diagram

Results

Of 66 patients included in the study, 5 controls died on the 5th and 6th days and were therefore excluded from the study [Figure 1]. Finally, the data of 33 patients in the intervention group and 28 patients in the control group were analyzed using the per-protocol method. The mean age of patients in the control and the intervention groups were 33.7 ± 12.1 and 33.2 ± 11.9 years, respectively (P = 0.854). The two groups were also homogenous respecting their baseline characteristics such as sex, marital status, comorbid disorders, cause of trauma, type of brain injury, and having surgery to remove a brain hematoma (P > 0.05) [Table 1]. All patients in the two study groups were under mechanical ventilation through SIMV mode and received midazolam, fentanyl, and morphine with no significant difference (P > 0.05).

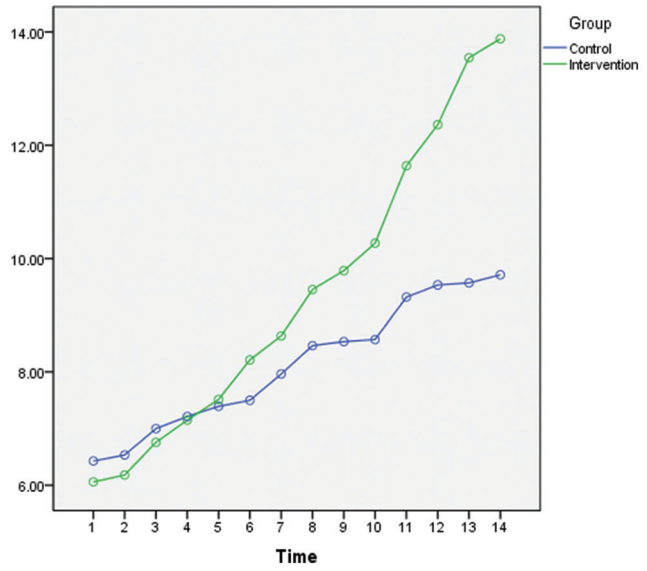

Figure 2: Comparison of Glasgow Coma Scale score between the intervention and control groups

The control and the intervention groups were not significantly different in terms of their baseline mean GCS score (4.3 ± 0.4 vs. 4.2 ± 0.4, P = 0.157), FOUR score (6.06 ± 0.93 vs. 6.42 ± 1.16, P = 0.177), and the duration of mechanical ventilation (22.43 ± 14.47 vs. 26.42 ± 16.39, P = 0.132). However, the control and the intervention groups were significantly different in their baseline APACHE II score (17.9 ± 1.3 vs. 18.9 ± 1.6, P = 0.011).

In the repeated-measures analysis, the sphericity was met neither for GCS nor for the FOUR score (P < 0.001), then the Greenhouse–Geisser test was used and showed that over time, the royal jelly significantly increased the mean GCS [F = 13.79, df = 1, and P < 0.001; Table 2 and Figure 2] and FOUR score [F = 13.08, df = 1, and $P \leq 0.001$; Table 3 and Figure 3]. However, significant interactions were observed between time and the mean GCS scores (F = 30.72, df = 2.317, and P = 0.001) and FOUR scores (F = 26.46, df = 2.69, and P = 0.001) in the two groups. Given the observed interaction, the t-test was used to conduct pairwise comparisons between the mean GCS and FOUR scores of the two groups at different times. As illustrated in Tables 2 and 3 and Figures 2 and 3, the intervention group

Table 2: Comparison of the mean Glasgow Coma Scale scores between the intervention and control groups during the study

Days	Mean±SD		*P* value (*t*-test)	Repeated measures analysis of variance		
	GCS in intervention group	GCS in control group		Test of within-subjects' effects (time×group) (Greenhouse-Geisser)	Test of within-subjects' effects (time) (Greenhouse-Geisser)	Test of between-subjects' effect
1	4.39±0.61	4.82±0.77	0.157	df=2.317	df=2.317	df=1
2	4.48±0.61	4.93±0.77	0.015	*F*=30.72	*F*=164.53	*F*=13.79
3	4.90±0.84	5.10±0.83	0.361	*P*<0.001	*P*<0.001	*P*<0.001
4	5.21±0.82	5.17±0.90	0.88			
5	5.54±0.97	5.32±0.94	0.367			
6	6.09±1.07	5.50±1.0	0.031			
7	6.39±1.11	5.82±1.22	0.061			
8	6.90±1.31	6.25±1.46	0.068			
9	7.15±1.56	6.35±1.52	0.49			
10	7.72±1.82	6.50±1.62	0.008			
11	9.15±2.25	7.17±2.04	0.001			
12	9.90±2.03	7.42±2.28	0.001			
13	11.45±2.26	7.60±2.46	0.001			
14	11.93±2.41	7.60±2.51	0.001			

GCS: Glasgow Coma Scale, SD: Standard deviation

Table 3: Full outline of unresponsiveness score comparison between the intervention and control groups during 14 days of intervention

Days	Mean±SD		*P* value (*t*-test)	Repeated measures analysis of variance		
	FOUR in intervention group	FOUR in control group		Test of within-subjects' effects (time×group) (Greenhouse-Geisser)	Test of within-subjects' effects (time) (Greenhouse-Geisser)	Test of between-subjects effect
1	6.06±0.93	6.42±1.16	0.177	df=2.69	df=2.69	df=1
2	6.18±0.98	6.53±1.20	0.211	*F*=26.46	*F*=158.85	*F*=13.08
3	6.75±0.83	7±1.08	0.328	*P*<0.001	*P*<0.001	*P*<0.001
4	7.15±0.90	7.21±1.10	0.808			
5	7.51±1.27	7.39±1.22	0.706			
6	8.21±1.47	7.50±1.26	0.049			
7	8.63±1.63	7.96±1.55	0.107			
8	9.45±1.98	8.46±1.59	0.038			
9	9.78±2.04	8.53±1.71	0.013			
10	10.27±2.26	8.57±1.79	0.002			
11	11.63±2.23	9.32±2.01	0.001			
12	12.36±2.26	9.53±2.37	0.001			
13	13.54±2.51	9.57±2.37	0.001			
14	13.88±2.57	9.71±2.40	0.001			

FOUR: Full outline of unresponsiveness, SD: Standard deviation

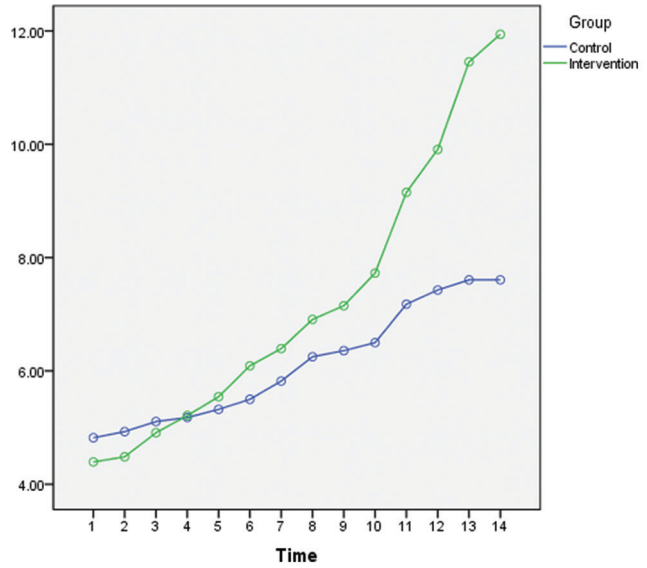

Figure 3: Comparison of FOUR Score between the intervention and control groups

experienced a greater increase in both variables, and the mean GCS at times 2, 6 and 9–14 and FOUR scores 6 and 8–14 were significantly different between the two groups ($P < 0.05$).

Because the disease severity (i.e., the baseline APACHE scores) was identified as a confounding variable, ANCOVA was conducted and the APACHE II score was entered into the model as a covariate. The results showed that the disease severity could not predict the changes in GCS [$P = 0.178$, Table 4] and FOUR score ($P = 0.384$) [Table 4].

Discussion

The results of this study showed that using royal jelly could significantly increase the LOC in patients with TBI. Such an improvement was evident in the increases observed in both the GCS and FOUR scores. Several nonpharmacological strategies have been used to improve the LOC in patients with TBI.[18-20] Royal jelly has also been used as a complementary treatment in several neurological disorders.[21,22] Various therapeutic properties have been reported for royal jelly. Some studies reported the effect of royal jelly in relieving menopause symptoms and aging-related diseases.[11,23] In another study, the use of royal jelly improved stress-induced and depression-like behavior.[24] Some studies also showed the positive effects of royal jelly on human cognitive and neurological functions.[10,11,22] Preclinical findings also showed that royal jelly promotes brain cell survival, improves cognitive functions, and enhances memory in Alzheimer's disease,[25] multiple sclerosis,[21] and Parkinson's disease.[11] A study also reported that royal jelly positively affected workers' longevity and memory-related traits.[26] However, few studies have been performed on the mechanisms through which royal jelly affects the neurological system, and most studies have been performed on laboratory models.[4,27] There are several ingredients in royal jelly among them 10HDA and Adenosine monophosphate N1 oxide are the two most important, with strong antioxidant and neurogenesis properties.[4,8] A study also reported that royal jelly might improve brain neural edema and apoptosis[27] and both of these properties might have a role in the improvement of the LOC after TBI. All the aforementioned studies are in

Table 4: Subgroup analyses of the effect of disease severity on changes occurred in Glasgow Coma Scale and full outline of unresponsiveness score

Model	Type III sum of squares	df	Mean square	*F*	Significance	Partial eta squared
GCS						
Corrected model	305.223	3	101.741	17.279	0.000	0.476
Intercept	94.999	1	94.999	16.134	0.000	0.221
Group	34.983	1	34.983	5.941	0.018	0.094
Group×pretest GCS×APACHI	20.928	2	10.464	1.777	0.178	0.059
R^2, adjusted R^2			0.476, 0.449			
FOUR score						
Corrected model	289.970	3	96.657	16.206	0.000	0.460
Intercept	122.636	1	122.636	20.562	0.000	0.265
Group	5.347	1	5.347	0.896	0.348	0.015
Group×pretest FOUR score×APACHI	27.265	2	13.633	2.286	0.111	0.074
R^2, adjusted R^2			0.460, 0.432			

GCS: Glasgow Coma Scale, FOUR: Full outline of unresponsiveness, APACHE II: Acute Physiology and Chronic Health Evaluation II

line with the present study and show the positive effect of royal jelly on the brain's functions and LOC.

All patients in the present study received sedatives, which made it difficult to assess the LOC. Although we assessed the LOC at least 4 h after receiving sedatives and performed random allocation to minimize this effect, further studies are yet needed in this area. Furthermore, most of the participants in this study were males; therefore, further studies on female patients might be beneficial to confirm the results of this study.

Conclusion

This study showed that the use of royal jelly improves the LOC of patients with TBI. Therefore, physicians and nurses caring for these patients are suggested to use royal jelly as a dietary supplement in patients with TBI to help improve their LOC and enhance the process of recovery in these patients.

Acknowledgment

This article was derived from a master thesis of Nursing with project number (A-11-148-22) Zanjan University of Medical Sciences, Zanjan, Iran. The authors would like to acknowledge the research deputy at Zanjan University of medical sciences for their support. We also are thankful of all patients who participated in this study.

Financial support and sponsorship

This study was financially supported by Zanjan University of Medical Science. This article was derived from a thesis research project.

Conflicts of interest

There are no conflicts of interest.

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