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The Efficacy of Sedation Depends on the Diet of Population

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Abstract

Physicians are often faced with the fact that the duration of anesthesia varies in different patients, which significantly complicates the process of surgical intervention and may confront the surgeon with an unforeseen situation. Recently, publications have appeared in the literature on the effects of various, including exotic products on anesthesia. There are also many conflicting statements about the effect of camel milk (CM) on the duration of anesthesia. Some data show that CM prolongs anesthesia, while other scientists argue the exact opposite: CM shortens the effect of the anesthetic. We decided to shed light on these studies by analyzing the effect of CM consumption on the effectiveness of local anesthesia in different patients. This article highlights the significant changes that occur in anesthesia due to the patients' diet. To achieve the set goal, we sort the twenty patients underwent local anesthesia into groups depending on the habit of using CM. The first, control, group consisted of practically healthy patients who did not use CM throughout their lives, and the second group had the habit of regularly taking CM. In both groups, local anesthesia was first performed without pre-drink CM. For the second time, participants in the control and experimental groups were asked to drink CM before the anesthesia procedure. Both in the control and experimental groups, patients drank CM one hour before local anesthesia. A significant correlation was found between the use of CM and the duration of anesthesia in both groups. Consumption of CM had a different effect on the duration of local anesthesia in the experimental and control groups. When milk was consumed before the use of analgesics in these two different groups, it changed exactly the opposite: for those who usually drink milk, it was shortened, and for those who did not drink it daily, lengthened. Thus, we found that the differences in the statements of scientists about the CM impact on anesthesia are based on the fact of different effects of CM in its single and long-term use. We attribute this to the suppression under long-term use of CM the cytochrome system neutralizing both foreign compounds and nutrients entering the organ. However, further long-term studies with larger sample sizes are needed to elucidate the molecular mechanisms behind this phenomenon.

Keywords

Camel Milk, Cytochromes, Anesthesia Duration

1. Introduction

Camel milk (CM) is a commonly consumed diary product in Arab countries. It is acknown that the CM differs from bovine in composition. Thanks to CM irreplaceable properties, in some countries, it is considered a traditional drink which is believed to be even the primary source of nutrition in Arab countries.

1.1. CM Unique Composition

It is routinely consumed daily, as it is low in cholesterol and sugar, but high in minerals. CM as a nutrient with a rich chemical composition: it comprises protective proteins, such as immunoglobulins, lysozyme, β-lactoglobulin, lactoferrin [1] [2], lactoperoxidase, etc. β-lactoglobulin of CM is unique in terms of antioxidant factors; lactoferrin of CM has the ability to inhibit the cancer cells development. It is rich in panthotenic acid, folic acid, niacin and cobalamin. CM is also pronouncedly high in vitamin C, while vitamin A and riboflavine is lower than in bovine milk. [1] [3] [4]. As about vitamin C, its level is in average three times higher than that of cows milk [2]. Few clinical trials have suggested that vitamin C in CM is in such high doses, that negates anesthesia in patients who consume it [5]. CM is prooved to have antibacterial, antiviral, antifungal, antihepatitis, antiarthritic effects. These medicinal properties of CM have been published in literature as aiding in the treatment of paratuberculosis, prevention of aging, and a remedy for autoimmune diseases and has a cosmetic value as well [5] [6] Camel milk contains a large amount of α-hydroxy acids, which make the skin smooth and is used to treat skin conditions such as eczema, psoriasis, different forms of dermatitis, acne, and so on [1] [6]. Creating hypoglycemia, the insulin in CM that is safe, can be an effective tool for improving long-term glycemic control in diabetic patients. The other cited benefits are their ability to reduce autism symptoms in children; and its rich magnesium and zinc content exhibits anti-ulcer properties. The higher levels of iron content are believed to prevent osteoporosis and anemia. CM comprises lactose composed of two sugars, which are fermented to lactic and pyruvic acid when milk goes sour [7]. Researchers have isolated new strains of lactic acid bacteria from raw CM that kill even very large numbers of different pathogens [8]. Additionally, the fermentation and enzymatic hydrolysis of camel protein produce different types of bioactive peptides exerting different activities in *in vitro* and *in vivo* [9] [10]. It also includes fat that is considered to be small in quantity [11], and thart fact would be useful to consider for those who do not want to gain weight, but want to have a healthy body with a healthy skeleton. Since it has a significantly different chemical make up, it does not cause cow milk intolerance reactions [9].

1.2. CM Impact on Sedation

Evidence is clear that all known xenobiotics begin their path of detoxification in the liver with modification in the hydroxylation reaction when the most hydrophobic compounds, in particular anesthetics, are converted into hydrophilic ones. Vitamin C with hydroxylases is involved in microsomal oxidation (hydroxylation) reactions, and helps to introduce a polar hydroxyl group to a number of compounds, ergo its high doses in CM stimulate this type of reactions leading to early elimination of anesthetic and shorten its pain relief effect. Due to this, world widely considers CM an enemy in medical field. Recently, a lot of scientific work has been carried out to improve understanding of its ingredients action mechanism [6].

As it has already been mentioned above, CM is traditionally used by population of southern countries. The data available in the literature about the CM influence on anesthesia are very contradictory, which requires additional researches in this field. Due to that, it's vital to be aware of its effect on anesthesia. It is necessary to adapt the technique chosen for the CM user patients and to develop specific skills for the team that administers anesthesia them [12] [13] [14]. We set ourselves the task of shedding light on the change in the anesthesia duration under the CM action in various categories of people.

2. Study Design

2.1. Subject of Investigation

The research & Ethic Committee along with Ministry of Health and Prevention, Research Ethics Committee/RAK Subcommittee (MOHAP/REC/2019/37-2019-UG-D) have approved this research of RAK Medical Health and Sciences University (RAKMHSU-REC-83-2018-UG-D) conducted in 2018.

Inclusion criteria: All patients older than 19 healthy and over 19 years of age without allergy to the investigated anesthetic were included in the study.

Exclusion criteria: All patients with congenital and acquired metabolic disorders, particularly with liver failure and history of excretory (kidney) disorders.

A study with a total number of 20 patients subdivided into groups of 10 in each was carried out. Patients aged 18 to 55 required local anesthesia before a dental procedure. The first group of ten medically fit control group participants consisted of patients that did not consume CM in their lifetime. The second group was the experimental group, comprised of ten medically fit patients consuming CM routinely. An initial consent form was obtained from all the patients. Arabic speaking and non-Arabic speaking participants in the control group were randomly similar in number 50% for each sort. Still, in the experimental group, the Arabic, speaking participants were more than non-Arabic speaking: 60% against 40% non-Arabic.

2.2. Procedure Done

The co-investigator distributed the questionnaires to the patients to fill in. They were informed of the research study in-depth and were allowed to clarify doubts. They were informed that the anesthesia time would be measured; and they were to fill the questionnaire provided after the procedure. Each group was tested for sensitivity to anesthesia twice: after drinking the milk and before milk consumption before tooth extraction. A sensitivity test was done for anesthesia before extraction (an intradermal test with 1% lidocaine without preservatives was considered negative if no erythema, induration, blistering, and itching observed 48 hours later). At the first step, the dental extraction was carried out in both groups by ensuring that the patient had not drunk the CM for two days. We performed a similar procedure twice with each patient at different times to avoid the influence of random factors on the studied parameter, after which patient mean values were calculated. These indicators were considered their parameters for the anesthesia duration. Patients were prepared for dental extraction per the protocol of infection control for extraction procedures.

At the second step of investigation, the control group patients (never used CM) and constantly drinking CM (experimental group) came for their second tooth extraction. No instructions were given to stop CM for two days in routine CM drinkers. At that step the same, control and experiment participants, were given 280 ml of CM one hour before local anesthesia. These patients were given pasteurized CM since the Central Veterinary Research Laboratory in UAE informed, that raw camel milk is illegal to be given. The second stage of the study was also duplicated, and the average value calculated from these two visits taken as an indicator of patient's anesthesia duration. The full anesthesia was standardized (only one cartridge of Lidocaine 2% + epinephrine 1:100,000); the type of anesthesia was infiltration. The effect and duration of anesthesia were tested as in Blazer MM et al. technique, 2015 [15].

The statistical analysis was carried out using İBM SPSS version 26 with 95% confidence.

3. Results

Distribution of patients without CM consumption before extraction according to the duration of anesthesia (in hours) in the control group, regardless of the sex of the studied persons shows that mainly, the anesthesia duration in this case is within 2 hours. In the control group in case of milk CM one-time take before anesthesia, the anesthesia duration was in average within 2 - 5 hours. To be correct, the initial anesthesia duration mean in the control group without CM was 1.925 ± 1.13 (1.12; 2.73) hours (**Table 1**), while with CM this figure shifted to 3.05 ± 1.52 (1.96; 4.14) hours (**Table 2**), showing a significant difference in this parameter depending on CM action. So, the control group showed a considerable shift after camel milk consumption compared to the first step of investigation, *i.e.* the duration mean change was positive (+58%), *i.e.* prolonged.

Table 1. The main parameters of the control group patients who did not drink milk before anesthesia.

Without milk (Control Group)			
Parameters		**Statistics**	**Standard Error**
Mean		1.93	0.36
95.0% Confidence interval for mean	Lower board	1.12	
	Upper board	2.73	
Mean truncated by 5%		1.90	
Median		2.00	
Mode		2.00	
Sample Variance		1.28	
Standard Deviation (σ)		1.13	
Minimum		0.25	
Maximum		4.00	
Range		3.75	

Table 2. The main parameters of the control group patients who took milk before anesthesia.

With milk (Control Group)			
Parameters		**Statistics**	**Standard Error**
Mean		3.05	0.48
95.0% Confidence interval for mean	Lower board	1.96	
	Upper board	4.14	
Mean truncated by 5%		3.06	
Median		2.75	
Mode		2.00	
Sample Variance		2.30	
Standard Deviation (σ)		1.52	
Minimum		1.00	
Maximum		5.00	
Range		4.00	

As for the anesthesia duration in patients of the experimental group, at first step of investigation the anesthesia duration in these patients regardless of gender was approximately 4 hours (Table 3: Mean = 3.55), while in case CM consumption before extraction, the anesthesia duration shortened to nearly 2 hours. To be correct, the mean of the experimental group anesthesia duration without camel milk was 3.55 ± 0.69 (3.06; 4.04) hours (Table 4), and with milk this indicator shifts to 1.75 ± 0.29 (1.54; 1.96) (Table 5), indicating significant lowering of anesthesia efficacy in this group after CM consumption.

Table 5 shows that the change in the experimental group anesthesia duration after CM consumption is significant at $P < 0.0001$ level.

Quite the opposite compared to the control group, in the experimental group when drinking camel milk immediately before anesthesia, the duration of anesthesia was was negative (−51%). The changes in the percentage within the groups (+58% in control group and −51% in the experimental group) show the dependence of milk effect to anesthesia on body reticuloendothelial system previous life experience with CM: the percentage actually decreased due to CM drinking in the experimental group, but raised in the control group. Such variations in this parameter in two separate groups show that CM may dramatically shorten or lengthen the duration of anesthesia depending on population type: consuming/not consuming the camel milk.

We found also a noticeable difference between the initial duration of anesthesia in CM user/non-user populations (Table 6).

We were able to establish significant changes in opposite directions after using CM. Comparing the duration of routine anesthesia without milk in the first and second groups, we may note that the basal lasting of anesthesia is about 2 hours in the control group and nearly 3 hours and a half, in the second group.

Table 3. The main parameters of the experimental group patients who did not drink milk before anesthesia.

Without milk (Experimental Group)			
Parameters		**Statistics**	**Standard Error**
Mean		3.55	0.22
95.0% Confidence interval for mean	Lower board	3.06	
	Upper board	4.04	
Mean truncated by 5%		3.56	
Median		3.75	
Mode		4.00	
Sample Variance		0.47	
Standard Deviation (σ)		0.69	
Minimum		2.50	
Maximum		4.50	
Range		2.00	

Table 4. The main parameters of the experimental group patients who took milk before anesthesia.

With milk (Experimental Group)			
Parameters		**Statistics**	**Standard Error**
Mean		1.75	0.09
95.0% Confidence interval for mean	Lower board	1.54	
	Upper board	1.96	
Mean truncated by 5%		1.76	
Median		1.88	
Mode		2.00	
Sample Variance		0.08	
Standard Deviation (σ)		0.29	
Minimum		1.25	
Maximum		2.00	
Range		0.75	

Table 5. The anesthesia duration differences reliability due to use CM in the experimental group.

Indicator	Value
t-statistic	10.86
DF	9
Significance level	P < 0.0001
95% CI for mean	3.18 to 3.93

Table 6. The significant difference in the initial anesthesia duration between the control and experimental group.

Difference	1.63
Standard error	0.418
95% CI	0.75 to 2.50
t-statistic	3.89
DF	18
Significance level	P = 0.0011

As the results have shown, there was a highly significant difference between the control and experimental group initial anesthesia duration (without milk drinking before procedure) and after procedure (with milk drinking before anesthesia). We have statistically proved, that a camel milk significantly affects the duration of anesthesia (correlation coefficient r = 0.838). So we state that there is a very strong correlation between, on the one hand, the camel milk single-time drinking and anesthesia efficacy, and on the other hand, the lifelong CM consumption and anesthesia duration. The data on the correlation between the one-time CM consumption before the procedure and the duration of anesthesia are also confirmed by the following. When comparing data patients without milk with data patients taking milk before the procedure, Pearson's chi-square was 63,333 and $P < 0.01$.

Therefore, doctors should bare in mind and warn their patients that drinking a CM before the procedure impacts the duration of the anesthesia significantly. As for extraction procedure, it is of great importance for the patient how long the blockage of innervation lasts: on average the difference in the duration of anesthesia for each individually taken person is approximately hour and a half. We note that we found out the negative correlation between constant milk consumption and anesthesia duration in the experimental group; so whenever the patient has been consuming CM for a long time, the anesthesia duration is significantly lowered when drinking milk just before anesthesia.

4. Discussion

The results showed a robust correlation between the CM single-time drinking and the lifelong consumption and anesthesia efficacy. We found out that the duration of anesthesia after camel milk drinking was lowered for more than 80% in patients with longlife CM consumption, re-confirming Dr. Hinkle and other researches' previously published data in this field [11]. When the anesthesia duration after milk drinking were measured, we found out that created by lidocaine 2% + epinephrine 1:100,000 mixture anesthesia [16] [17] had been lasting for 1.25 - 2 hours, what was opposite to Dr. Stanley, Dr. Sean and Dr. Paulon ideas, who constatate that it is usually lasting around 1 - 5 hours [18] [19].

As may be seen, the scientists around the world are trying to understand the reason for the differences in patient response to anesthesia when it comes to drinking milk, but to no avail. Significant opposite changes after drinking camel milk show that there is a clear evidence of the dual effect of camel milk on patients. In those who drank milk for the first time before anesthesia, the duration of the drug's action is prolonged. And vice versa, in those who drank milk constantly and additionally took it before anesthesia, the time of anesthetic effect is reduced. Since in the body of patients who do not consume CM initially, before the use milk one-off time, anesthesia has lasted for significantly less hours than in the second group, it can be assumed that this is most likely the result of more active work of their cytochrome microsomal systems. Perhaps after drinking milk, in the body of such patients, some component of CM blocks the detoxification system, which is why the duration of anesthesia in them lasts much longer than in the second group after drinking milk. The average 3.55 hours duration of anesthesia in this group of patients (second group) demonstrates significant lifelong suppression of their microsomal oxidation system. Results obtained by Ibrahim Z. and co-authors showed, that camel milk suppresses the mRNA expression of cytochrom P 1A1 (CYP1A1), as well as CYP1A2, CYP3A2 and CYP2B1, that participate in modification and detoxification of xenobiotics [20].The authors assume that through this suppressive effect, a CM has a potential anti-cancer effect due to procarcinogenes to carcinogens activation prevention. Our data coincoil with these data, where the liver cytochrome P system was found to be supressed by CM components. The reason for decreased anesthetic effect in CM consuming patients (second group+ CM) may be explained by the relatively high dose of vitamin C in this nutrient which results in early detoxification of lidocaine by modification of its structure with hydroxylases. So, this may be the main mechanism of acceleration by vitamin C detoxification in patients with suppressed CYP system. There are some mechanisms in this system that get used to working in tension mode, which helps it to accelerate significantly with only 280 ml of milk. We state that most likely, the real reason for the sharp decrease in the duration of the anesthetic action in patients who use CM a daily basis is high dose of vitamin C present in camel milk. Acceleration of detoxification in patients with CYP system suppression may also be the result of an adapted vitamin C-dependent activation of another, bypassing the CYP pathway of xenobiotics detoxification in these patients. Due to this, those accustomed to drinking CM, with help of vitamin C high concentrations quickly modify and eliminate chemical reagents, including anesthetics, which leads to a shortening of the anesthesia duration in them after milk drinking.

It is acknown that vitamin C may perform hydroxylation reactions by pathway different from microsomal oxidation (**Figure 1**), which is why most probably modification of pain killer (lidocaine) was made earlier after drinking milk in the second group used to consuming camel milk.

As for the control group, their microsomal systems work as usual, without suppression, leading to relatively early modification of anesthetic, which is why we observe that the anesthesia duration has been lasting for minimal, 1.925 hours. When CM is given just before anesthesia to patients not in the habit of CM consumption, the suppressive action of peptides on the cytochrome system has not been manifested yet, as it takes a longer duration to achieve this effect. Therefore, the reason of prolonged anesthetic circulation in the blood and its action in the control group after one-time CM consumption is, most probably, the action of some milk components on the detoxification system not at the mRNA level, but by the blokage of some enzyme systems way, as the control group patients enzyme systems are not accustomed to contact with new milk protein components. This is akin to an allergic reaction, when a new allergen entering the body triggers the body's defense systems toward allergen, ergo the other foreign component (in our case, an anesthetic) may freely manifest its activity prolonged. The inhibition of drug detoxification and decrease in its elimination after CM ingestion in such kind of population (not drinking CM daily + one-time CM) occurs not at the level of gene repression, but at the level of inhibiting enzyme systems. So, those who do not consume milk in everyday life react to it as to an allergen, which leads to a decrease in the activity of protective detoxifying enzyme systems and a delay in eliminating of the pain reliever from the body, followed by prolonged anesthetic action.

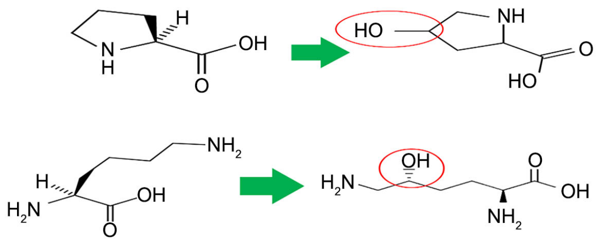

Figure 1. Vitamin C as cofactor of proline hydroxylase & lysyl hydroxylase adds an alcohol group to lysine forming hydroxyproline and hydroxylysine respectively [21].

Finally, we state that camel milk may reduce or increase the duration of anesthetics action depending on person's enzyme system preliminary contact with this milk. As it is obviously seen from this study, we need to highlight the importance of dealing with patient who are CM consumers with cautious. Without any doubt, we have identified significant deviations from the generally accepted data in the duration of anesthesia, which require further research to identify the detailed mechanism of these deviations on vitamin C dependent enzyme systems different from CYP. Due to CM valuable biological and nutritional properties [22], its use in diet and medicine will rise, but its dual effect on sedation must be taken into account.

5. Conclusions

- Without milk consumption before anesthesia, initial analgesic effect is significantly longer in the group of patients constantly using camel milk (3.55 h).
- After drinking camel milk before anesthesia, the duration of anesthesia changes both for those who use it daily and for those who drink it for the first time.
- The anesthesia duration has been changed exactly opposite when drinking milk before using analgesics: lengthened in those who do not drink it routinely and shortened in those who usually drink milk.
- The authors recommend taking a dietary history before procedures requiring anesthesia in these patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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