

# A pilot study for the relationship between habitual dietary caffeine consumption and intraoperative analgesic requirements in patients undergoing laparoscopic surgeries

## Relación entre consumo de cafeína y requerimiento analgésico luego de cirugía laparoscópica

Raham Hasan Mostafa<sup>1,\*</sup>, Ashraf Nabil Saleh<sup>1</sup>, Shaimaa M.S. Rakhia<sup>1</sup>, Ahmed Mohamed Khamis<sup>1</sup>

<sup>1</sup> Department of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University. Cairo, Egypt.

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### ABSTRACT

**Background:** The most used psychoactive substance worldwide is caffeine. Acute caffeine administration in a laboratory setting or caffeine as an adjuvant have been shown to have pain-relieving effects. The possible effects of habitual dietary caffeine consumption on the use of intraoperative analgesics and pain perception, however, are far less well understood. **Methods:** Design: A prospective observational exploratory pilot study. Setting: Single university teaching hospital's operating rooms. **Patients:** After institutional approval of the study design, 90 surgical patients - scheduled for laparoscopic surgery- were surveyed about their average daily caffeine consumption. They were then grouped to either: non consumers, low caffeine consumers and high caffeine consumers. **Objectives:** This pilot study aimed to explore the relationship between the amount of daily dietary caffeine consumption and intraoperative analgesic requirements. **Results:** In this study, no significant difference was found between the three study groups as regard intraoperative analgesic requirements, hemodynamics, recovery time, postoperative headache, and postoperative sedation level. However -although statistically insignificant- both caffeine consumers groups had higher intraoperative analgesic consumption. Additionally, higher consumer group had earlier request time of postoperative 1st rescue analgesia. **Conclusion:** Despite the limitations of any pilot study, our results suggest that habitual caffeine -whether in low or high consumers- had no significant effect on intraoperative analgesic requirements, when compared to non-consumers group. The data presented require careful consideration and promote the need for further studies with larger sample size as our study is an exploratory pilot study with small sample size.

**Key words:** Laparoscopic surgery, caffeine, adenosine, analgesia, pain.

### RESUMEN

La sustancia psicoactiva más utilizada a nivel mundial es la cafeína. Se ha demostrado que la administración aguda de cafeína en un entorno de laboratorio o la cafeína como adyuvante tiene efectos analgésicos. Sin embargo, los posibles efectos del consumo habitual de cafeína en la dieta sobre el uso de analgésicos intraoperatorios y la percepción del dolor son mucho menos conocidos. **Métodos:** Diseño: Estudio piloto prospectivo observacional exploratorio. Lugar: Quirófanos de un hospital docente universitario único. **Pacientes:** Después de la aprobación institucional del diseño del estudio, se encuestó a 90 pacientes quirúrgicos, programados para cirugía laparoscópica, sobre su consumo promedio diario de cafeína. Luego se agruparon en: no consumidores, consumidores bajos de cafeína y consumidores altos de cafeína. **Objetivos:** Este estudio piloto tuvo como objetivo explorar la relación entre la cantidad de consumo diario de cafeína en la dieta

rahamhasan@yahoo.com

\*ORCID: <https://orcid.org/0000-0002-5560-2733>

por los requisitos analgésicos intraoperatorios. **Resultados:** En este estudio no se encontró diferencia significativa entre los tres grupos de estudio en cuanto a los requerimientos analgésicos intraoperatorios, hemodinámica, tiempo de recuperación, cefalea posoperatoria y nivel de sedación posoperatoria. Sin embargo, aunque estadísticamente insignificante, ambos grupos de consumidores de cafeína tuvieron un mayor consumo de analgésicos intraoperatorios. Además, el grupo de consumidores más alto solicitó antes la primera analgesia de rescate posoperatoria. **Conclusión:** A pesar de las limitaciones de cualquier estudio piloto, nuestros resultados sugieren que la cafeína habitual, ya sea en consumidores bajos o altos, no tuvo un efecto significativo sobre los requerimientos analgésicos intraoperatorios, en comparación con el grupo de no consumidores. Los datos presentados requieren una cuidadosa consideración y promueven la necesidad de estudios adicionales con mayor.

**Palabras clave:** Cirugía laparoscópica, cafeína, adenosina, analgesia, dolor.

Trial Registration: NCT05330754

## Introduction

Approximately 90% of all adults in the world consume caffeine in their daily diet. In 2015, the European Food Safety Authority (EFSA) suggested that up to a daily 200 mg from all caffeine sources do not raise safety concerns[1]. Caffeine and adenosine are structurally similar, which allows caffeine to bind to adenosine receptors, block adenosine, and inhibit its effects. Adenosine is known to inhibit arousal and increase drowsiness, as it is an inhibitor of neuronal activity in the peripheral and central nervous systems. In moderate doses, caffeine can antagonize the effects of adenosine and reduce fatigue and increase alertness[2]. Additionally, caffeine shows pain relieving properties by blocking peripheral adenosine receptors on sensory afferents. Because of this, it has been included in many over the counter and prescription drugs[3]. Despite these effects, caffeine at dietary levels is not usually regarded as an analgesic on its own with very few available clinical data.

Given the forementioned data, we hypothesized that dietary caffeine consumption would have favorable effects on perioperative analgesic consumption in laparoscopic surgeries with expected further decrease in analgesic needs in "high caffeine consumers" group. This study aimed to investigate the relationship between the amount of daily dietary caffeine consumption and intraoperative analgesic requirements.

## Materials and Methods

### Ethics

Ethical approval for this study (FMASU R 67/ 2022) was provided by the Ethics committee of university hospital on 19/4/2022. It also was registered at Clinical Trial Registry ClinicalTrials.gov Identifier: NCT05330754. Written informed consent was obtained from all applicants.

### Inclusion criteria

We enrolled ninety patients who were: 18 - 65 years old, physical status American Society of Anesthesiology (ASA) I&II, scheduled to undergo elective laparoscopic surgery.

### Exclusion criteria

Patients converted to an open surgery, and those with: psy-

chological or nervous system diseases, uncontrolled cardiac arrhythmias, addicts, or smokers.

### Patients' recruitment

Preanesthetic check-up was done. Average daily caffeine consumption in mg was calculated according to "caffeine content in consumed drinks" as estimated by "Food Data Central"[2],[4]. Products asked upon in the preanesthetic checkup were: regular/green coffee, instant coffee, espresso, decaffeinated coffee, black tea, green tea, cola drinks, energy beverages, dark chocolate, milk chocolate, and medication with caffeine. And accordingly, patients were grouped to one of 3 groups:

1. Control group: No caffeine intake.
2. Low caffeine consumers (Safe level) group: Caffeine daily intake  $\leq$  200 mg/day.
3. High caffeine consumers (Unsafe level group): Caffeine daily intake  $>$  200 mg/day.

The proposed classification is according to previous guidelines[1].

### Anesthesia and surgical procedure

Pre-oxygenation with 100% oxygen was done. General anesthesia was induced intravenously with propofol 2 mg/kg, fentanyl 1.5  $\mu$ g/kg, and atracurium 0.5 mg/kg to be followed by orotracheal intubation after 3 minutes of manual ventilation. After securing of endotracheal tube, all patients were positioned to start the surgery and the laparoscopic procedure was carried out in a standard fashion. 1%-2% (vaporizer setting) of isoflurane mixed with oxygen (50%) and air (50%) was used for maintenance of anesthesia. Increments of 10 mg of atracurium were administered repetitively every 20 minutes to achieve muscle relaxation. Minute ventilation volume was adjusted to keep end tidal  $PCO_2$  at 35 mm Hg to 40 mm Hg. Mean arterial blood pressure (MABP) and heart rate (HR) were measured at specific time points. MABP rise of  $>$  20% above baseline was treated by administering a 0.5  $\mu$ g/kg intravenous bolus of fentanyl. At the end of surgery and after closure of skin incision, residual neuromuscular blockade was reversed and extubation was done. The time of arrival in the postoperative unit is defined as 0 h postoperatively. A fixed dose of intravenous paracetamol 1 gm was given every 6 hours to all patients in both groups starting from 0 h in PACU.

**Patient reported outcomes**

The primary outcome was “total intraoperative fentanyl consumption in microgram”. (Induction dose was not included).

Secondary aims:

1. Recovery time in minutes (time interval between discontinuation of isoflurane and extubation).
2. Intraoperative hemodynamics: MABP and HR were recorded at the following timings: preoperatively as baseline, after intubation, after abdominal insufflation, then every 15 minutes till end of surgery, and then every hour for 2 hours in PACU.
3. Timing of 1st rescue analgesia (5 mg Nalbuphine).
4. Assessment of postoperative sedation level using “University of Michigan Sedation Scale (UMSS)”[5]. It was assessed every hour for 2 hours starting from extubation.

**Sample size**

As this trial is considered a pilot study, and given the lack of clarity on the ideal sample size due to lack of related information on the relationship between habitual dietary caffeine consumption and perioperative analgesic requirements; a sample size of at least 30 cases per group was considered appropriate.

**Statistical analysis**

The collected data was revised, coded, tabulated and in-

roduced to a PC using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) Shapiro wilk’s test was used to evaluate normal distribution of continuous data. Quantitative variables are expressed as mean and SD. Qualitative variables are expressed as frequencies and percent. ANOVA test was used to compare Quantitative variables between the three study groups. Post Hoc Test was used for comparisons of all possible pairs of group means. Chi square and Fisher’s exact test were used to examine the relationship between Categorical variables. Correlation analysis using Pearson/spearman’s method was used to assess the strength of association between two quantitative variables according to data distribution. A P-value < 0.05 was considered statistically significant.

**Results**

As regard personal data, there was no significant difference between the three study groups as regard age, gender, body mass index (BMI), sleeping hours and ASA-PS. Similarly, there was no significant difference between the three study groups as regard type of operation, duration of operation and recovery time (Table 1). As regard MABP and HR at baseline and at different follow up, no significant difference was found between the three study groups (Figure 1) (Figure 2). As regard analgesia, sedation and postoperative headache, no significant difference was found between the three study groups as regard total intraoperative fentanyl, timing of 1st rescue analgesia, sedation

**Table 1. Comparison between three groups as regard personal and medical characteristics**

	Group						P	Sig
	Control		Low consumers		High consumers			
	Mean	± SD	Mean	± SD	Mean	± SD		
Age (years)	41.77	10.70	43.87	12.18	39.50	11.28	0.337‡	NS
BMI	35.30	8.05	35.25	8.31	37.13	9.45	0.631‡	NS
Sleeping hours/day	7.57	1.07	7.30	.84	7.23	1.10	0.406‡	NS
Duration of operation (minutes)	95.00	19.43	91.50	20.39	93.00	18.22	0.782‡	NS
Recovery time (minutes)	8.67	3.92	9.17	3.49	9.50	3.79	0.687‡	NS
Gender							0.954*	NS
Male	11	36.7%	11.00	36.70	12	40.0%		
Female	19	63.3%	19.00	63.30	18	60.0%		
ASA-PS							0.527*	NS
ASA 1	19	63.3%	18.00	60.00	22	73.3%		
ASA 2	11	36.7%	12.00	40.00	8	26.7%		
Laparoscopy							0.77**	NS
Cholecystectomy	23	76.7%	23.00	76.70	20	66.7%		
Colostomy	1	3.3%	2.00	6.70	0	0.0%		
Gastric bypass	2	6.7%	1.00	3.30	3	10.0%		
Hernia repair	2	6.7%	2.00	6.70	2	6.7%		
Gastrectomy	2	6.7%	2.00	6.70	5	16.7%		

‡ANOVA test.

\*Chi-Square Tests.

\*\*Fisher exact test.

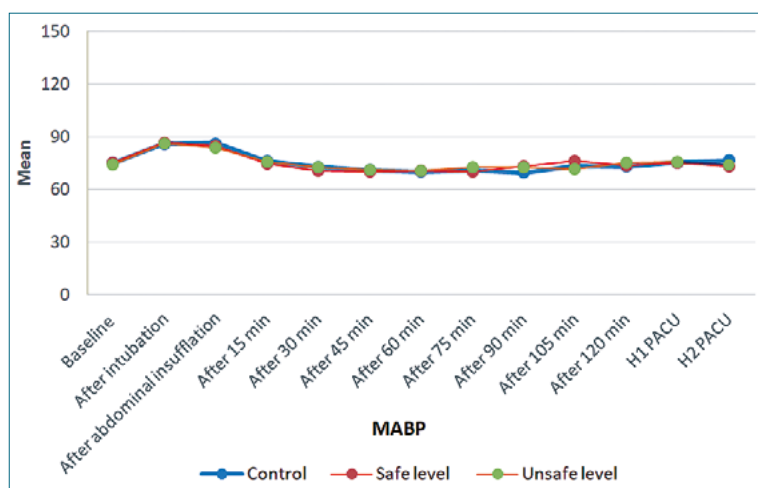


Figure 1. Comparison between three groups as regard MABP.

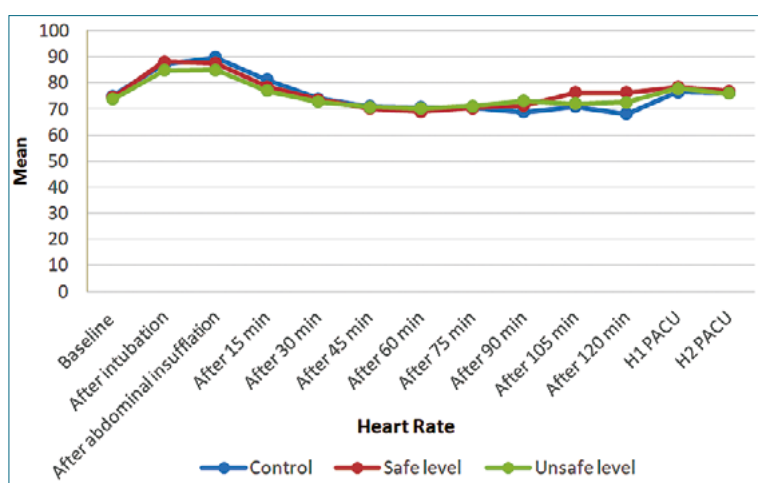


Figure 2. Comparison between three groups as regard HR.

score and post-operative headache (Table 2). There was no significant correlation between average total caffeine consumption per day and each of total intraoperative fentanyl, timing of 1st rescue analgesia, and postoperative sedation score (Table 3).

## Discussion

Caffeine administered acutely in a laboratory environment or as a medication adjuvant has known properties that help alleviate pain. Consistent evidence showed that antagonism of adenosine receptors by caffeine leads to decreased pain signaling in animal models for neuropathic, nociceptive, and inflammatory pain[6]. However, much less is known about the potential impact of habitual dietary caffeine consumption in relation to clinical pain alleviation. Exploratory pilot research is a methodology approach that explores research questions that have not previously been studied in depth. It is often used when the issue to be studied is new. In this exploratory pilot study, our observed results didn't support our expectation in confirming dietary caffeine analgesic potential. But since it is an exploratory pilot study, it could be beneficially considered as a hypothesis generating study that could be utilized by future

studies with larger sample size.

We observed that habitual caffeine -whether in low or high consumers- has no effect on intraoperative analgesic requirements, when compared to non-consumers group. We might contribute this observation to the following: 1- the development of caffeine tolerance due to habitual consumption might impact pain sensitivity through the upregulation of adenosine receptors[7]. 2- The effects of caffeine usually last from 8 to 12 hours[2]. But since surgical patients are often instructed to fast; they are at risk for experiencing fading of caffeine's effects (whether analgesic or stimulatory effects). 3- variable effect of caffeine on analgesic pathway[8]. The nociceptive effects of caffeine are associated with its nonselective antagonism of the adenosine A1, A2A, A2B and A3 receptor[3]. Adenosine has a dual nature in that it is a molecule that can cause and relieve pain via different adenosine receptors. Adenosine acts as an analgesic when acting through A1 receptors, which are central receptors, adenosine also contributes to chronic pain through its A2b receptors, which are peripheral receptors. This means that, caffeine's analgesic effect depends on which adenosine receptor was more blocked[8].

Noteworthy, although statistically insignificant, non-consumers group had marginal less intraoperative fentanyl re-

**Table 2. Comparison between three groups as regard analgesia, sedation and postoperative headache**

	Group						P	Sig
	Control		Low consumers		High consumers			
	Mean	± SD	Mean	± SD	Mean	± SD		
Total intraoperative Fentanyl (microgram)	170.00	33.73	178.33	31.30	180.00	31.07	0.436*	NS
Timing of 1st rescue (minutes)	90.33	28.74	92.41	35.45	83.50	23.53	0.481*	NS
UMSS H <sub>1</sub>							0.709**	NS
0	11	36.7%	16	53.3%	14	46.7%		
1	18	60.0%	13	43.3%	14	46.7%		
2	1	3.3%	1	3.3%	2	6.7%		
UMSS H <sub>2</sub>							1.00**	NS
0	30	100.0%	30	100.0%	29	96.7%		
1	0	0.0%	0	0.0%	1	3.3%		
PO headache							1.00**	NS
No	26	86.7%	25	83.3%	25	83.3%		
Yes	4	13.3%	5	16.7%	5	16.7%		

\*ANOVA test.

\*\*Fisher exact test.

**Table 3. Correlation between average total Caffeine consumption per day in mg and analgesic and sedation parameters**

		Total intraoperative Fentanyl	Timing of 1st rescue	UMSS H <sub>1</sub>	UMSS H <sub>2</sub>
Average consumption	Correlation coefficient	0.160*	-0.169*	0.141**	0.109**
	P	0.223	0.201	0.281	0.407
	sig	NS	NS	NS	NS

\*Pearson correlation.

\*\*Spearman correlation.

quirements when compared to either low or high consumers groups (170 ± 34 µg in non-consumers group, *versus* 178 ± 31 µg & 180 ± 31 µg in low and high consumers groups respectively). Additionally, earlier request of 1st rescue analgesia was observed in caffeine high consumers' group (83.50 ± 24 minutes in high consumers group, *versus* 90.33 ± 29 minutes & 92.41 ± 35 minutes in control and low consumers groups respectively). But it was also statistically insignificant. Since the current research protocol required subjects to fast for 8 hours preoperatively, it is likely that some subjects experienced caffeine withdrawal. Due to this acute abstinence of caffeine consumption, it is conceivable that some subjects may have been experiencing "caffeine withdrawal increased pain sensitization", which could be reflected in either higher intraoperative fentanyl consumption or earlier request of postoperative 1st rescue analgesia.

Antagonizing our results, previous studies[7],[9] showed that individuals who habitually consume greater amounts of caffeine as part of their daily diets demonstrate diminished sensitivity to painful stimuli in a laboratory setting. The results were the same whether subjects were abstaining caffeine before the procedure[9] or not[7]. These studies suggested that high dietary caffeine consumption may be sufficient to alter the

nociceptive processing of pain signals in ways that significantly decrease sensitivity to painful stimuli. On the other hand, Alo-baid and their colleagues[10], showed increased failure rates and delayed onset of local anesthetic among high caffeine consumers in fasting female patients undergoing dental procedure. This high failure rate could be attributed to caffeine's influence on cognitive performance by increasing alertness and augmented response to painful stimuli, as well as sleep deprivation caused by stress and anxiety[8]. Another interesting study by Karunathilake and their colleagues[11], performed baseline experimental pain testing and caffeine plasma concentrations (CPC) sampling on 30 healthy adults before and after surgical extraction of four third molars. Their study found that baseline pain sensitivity was higher among individuals who self-reported positive caffeine consumption. But on the other hand, caffeine seemed to have an antinociceptive effect postoperatively in individuals with CPC > 300 ng/mL.

Finally, surgical patients routinely fast preoperatively and may have postoperative symptoms from caffeine withdrawal. While there are several well-defined symptoms of caffeine withdrawal syndrome, the literature has focused on headache as the primary endpoint of assessing, preventing, and treating caffeine withdrawal. The onset of withdrawal symptoms typi-

cally occurs 12-24 hours after caffeine last intake but can occur as early as 3-6 hours post-ingestion especially in high consumers[12]. Unfortunately, this headache may be easily ascribed to other causes, masking the recognition of caffeine withdrawal as the causative source. In our study, postoperative headache symptom was not significant between the 3 groups. This could be attributed to variable causes of postoperative headache after general anesthesia which could mask the real prevalence of caffeine withdrawal headache.

Our study is not without limitation. Firstly, and most importantly, this is an exploratory pilot study. This means that our sample size might be too small to detect significant changes in the evaluated outcomes between the 3 groups. A sample size of at least 90 patients per group is recommended. Secondly, measurement error can affect the assessment of caffeine intake. As some beverages asked upon in the preanesthetic checkup were not brand or type specific. Additionally, coffee bean type, and the quantity of milk or cream added to coffee are typically not recorded. As a result, caffeine cannot be accurately quantified, and more research are needed with larger sample size and more accurate caffeine estimation in order to draw more obvious conclusions. Finally, preoperative chronic pain, analgesics, and anxiety disorders that affect perioperative pain was not recorded.

## Conclusion

Despite the limitations of a pilot study, our results suggest that habitual caffeine -whether in low or high consumers- had no significant effect on intraoperative analgesic requirements, when compared to non-consumers group. The data presented require careful consideration and promote the need for further studies with larger sample size as it is an exploratory pilot study with small sample size.

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