Review Article

Caffeine – Essentials for anaesthesiologists: A narrative review

Amit Kumar Malviya, Saranlal A M, Manish Mulchandani[1], Anju Gupta

Department of Anaesthesia, Pain Medicine and Critical Care, [1]Academic Section, All India Institute of Medical Sciences, New Delhi, India

Abstract

Caffeine has a multitude of uses in anaesthesia, and numerous studies have evaluated its efficacy and usefulness in various aspects of anaesthesia and medical practice. Its various applications in anaesthesia include its role in awakening from anaesthesia, managing post-dural puncture headache, managing post-sedation paradoxical hyper-activity in children, post-operative bowel paralysis, and apnoea in paediatric populations, that is, apnoea in infancy, paediatric obstructive apnoea, and post-anaesthetic apnoea in pre-mature infants. Though the effects of caffeine on bronchial smooth muscle, neurological, and cardio-vascular systems are well known, the relatively little-known effects on the endocrine and gastro-intestinal (GI) system have been recently taking primacy for eliciting its therapeutic benefits. The literature shows encouraging evidence in favour of caffeine, but unambiguous evidence of caffeine benefits for patients is lacking and needs further investigation. In this narrative review of literature, we summarise the available literature to provide insights into the pharmacokinetics, pharmacodynamics, clinical application of caffeine in modern anaesthetic practice, and evidence available in this field to date. An awareness of the various physiological effects, adverse effects, reported applications, and their evidence will widen the horizon for anaesthesiologists to increase its rational use and advance research in this field. Well-designed randomised controlled trials regarding the various outcomes related to caffeine use in anaesthesia should be planned to generate sound evidence and formulate recommendations to guide clinicians.

Keywords: Adult, anaesthesia, apnoea, caffeine citrate, cognition, critical care, infant, post-dural puncture headache, pre-mature, World Health Organisation

Introduction

Caffeine is an abundantly available pharmacological agent, which, apart from being used in medicine, is consumed in daily life in the form of coffee, tea, and soft drinks. Caffeine is generally used as a cognition and performance enhancer. It is an alkaloid naturally found in the seeds, fruits, nuts, and leaves of several plant species native to Africa, East Asia, and South America. Caffeine is commonly obtained from the seed of the coffee plant. It is commercially available as caffeine citrate for medicinal uses and is listed in the World Health Organisation's (WHO) model list of essential medicines.[1] Caffeine is regarded as a safe medicine by the US Food and Drug Administration as its toxic dose of over 10 grams per day for an adult is much higher than the typically prescribed dose of under 500 milligrams per day.[2] Various studies have tried to explore the use of caffeine in awakening from anaesthesia, prophylaxis and treatment of post-dural puncture headache, post-sedation paradoxical hyper-activity in children, post-operative bowel paralysis, and apnoea in paediatric populations, that is, apnoea in infancy, paediatric obstructive apnoea, and post-anaesthetic apnoea in pre-mature infants. This review is an attempt to summarise the role of medicinal uses of caffeine in anaesthesia and critical care.

Address for correspondence: Dr. Anju Gupta,
Department of Anaesthesia, Pain Medicine and Critical Care, Room No. 6, 4th Floor, Porta Cabin, Teaching Block, All India Institute of Medical Sciences (AIIMS), Ansari Nagar, New Delhi -110 029, India.
E-mail: dranjugupta2009@rediffmail.com

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_285_22

How to cite this article: Malviya AK, Saranlal AM, Mulchandani M, Gupta A. Caffeine – Essentials for anaesthesiologists: A narrative review. J Anaesthesiol Clin Pharmacol 2023;39:528-38.

Submitted: 06-Aug-2022 **Revised:** 31-Oct-2022
Accepted: 03-Nov-2022 **Published:** 12-Jan-2023

Data collection and search strategy

Combinations of relevant search terms such as caffeine, post-dural puncture headache, emergence from anaesthesia, paediatric apnoea, anaesthesia recovery, post-operative period, bowel paralysis, sedation, and paradoxical hyperactivity were searched in titles and abstracts available in the electronic databases PubMed (1056 results), Embase (1230 results), and Scopus (520 results). A total of 2806 results were obtained in this search. After removing duplicates, 858 articles were left. Abstracts of shortlisted papers available in the English language were read, and relevant papers (250 articles) were identified for full manuscript reading. All human studies assessing the effect of caffeine for desired clinical effects were included in the review. A few animal studies (58 articles) reflecting the mechanism of action of caffeine were included in the discussion. Details of relevant randomised controlled trials directly assessing the action of caffeine in at least one arm were summarised in the tabular form.

References of all identified papers were scrutinised to explore any of the articles which would have inadvertently got missed during the literature search. All such studies were assessed as per the above-described process.

Pharmacokinetics of caffeine

Routes and preparations: Caffeine is available as caffeine citrate for administration by oral and intravenous routes. Soluble formulations are also available for paediatric usage. The ratio of therapeutic doses of caffeine base to its citrate salt is typically 1:2.

Absorption: The oral bioavailability of caffeine is 100%. After oral ingestion, caffeine is almost fully absorbed within 45 minutes and the peak blood concentration is reached between 15 minutes and 2 hours. The rate of absorption of caffeine is slower if taken with meals. There is no significant first-pass metabolism, making the pharmacokinetics of caffeine independent of the route of administration. In adults, it has a variable half-life of 2.5–4.5 hours.[3]

Distribution: Caffeine is lipophilic and crosses all cellular membranes. It can be detected in all body fluids and secretions, and it readily crosses the placental as well as the blood–brain barrier.

Metabolism: Caffeine is primarily metabolised by microsomal enzymes, mainly CYP1A2 in the liver to form paraxanthine. Caffeine also induces microsomal enzymes and thus induces the metabolism of itself and other drugs. Neonates have a limited capacity to metabolise caffeine because of the immaturity of the hepatic microsomal system. Caffeine metabolism is significantly affected by smoking, concomitant medications, and pregnancy.

Excretion: The metabolites of caffeine are excreted through the urine, and only a minute fraction of caffeine is excreted unchanged.[4]

Pharmacodynamics of caffeine

The earliest proposed mechanism of action for caffeine involved the mobilisation of intra-cellular calcium (Ca^{++}). At high concentrations (1–10 mM), caffeine interferes with the uptake and storage of calcium in the sarcoplasmic reticulum of striated muscle and increases the translocation of Ca^{++} through the plasma membrane. Caffeine increases myofilament sensitivity to Ca^{++} through its binding to ryanodine receptors in calcium channels of muscle and brain.[5] Caffeine also releases calcium from the sarcoplasmic reticulum in skeletal and cardiac muscles.[5]

Caffeine is a nonselective phosphodiesterase inhibitor and results in increased intra-cellular cyclical adenine monophosphate ([cAMP]i) levels. Caffeine also shows an antagonistic action on all adenosine receptors [Figure 1 and Table 1].[6] However, the concentration at which caffeine inhibits phosphodiesterase is about 20-fold higher than the concentration at which it inhibits adenosine receptors.[7]

Physiological effects of caffeine on organ systems

Because of its diverse receptor action, caffeine produces a multitude of effects in our body [Figure 2]. Though the effects of caffeine on bronchial smooth muscle, neurological, and cardio-vascular systems are well known, the little-known effects on the endocrine and gastro-intestinal (GI) system are taking precedence for eliciting therapeutic benefits.

Neurological actions

a. Vigilance, cognition, and analgesia: Caffeine improves cognition and vigilance, though these are more pronounced

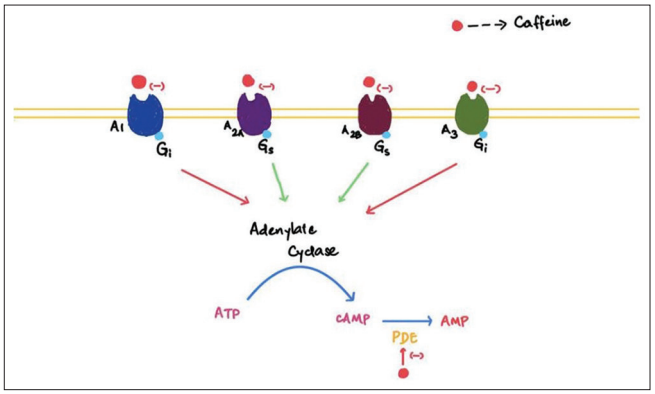

Figure 1: Caffeine, caffeine receptors, and mechanism of action. *ATP – Adenosine triphosphate, cAMP – cyclic adenosine monophosphate, PDE – phosphodiesterases, Gi/Gs – G protein-coupled receptors, A1/2a/2b/3 – adenosine receptors subtypes*

Table 1: Adenosine receptor, site of action of caffeine

Adenosine receptor/subtypes	Distribution	Function
A1	Throughout the body	Pre-synaptical reduction of synaptic vesicle release, reduction of heart rate, bronchial smooth muscle constriction
A2a	Cardiac tissue, brain	Vasodilatation of coronaries, decreases dopaminergic activity in CNS.
A2b	Bone tissue, bronchial smooth muscle	Osteoblast differentiation, bronchospasm
A3	Bone tissue	Down-regulation of osteoclasts

in sleep-deprived states. Caffeine can contribute to pain relief when used as an adjunct. A review of 19 studies showed that the addition of 100 to 130 mg of caffeine to an analgesic modestly increased the proportion of patients with successful pain relief.[8]

b. Sleep, anxiety, and hydration: Caffeine consumption increases sleep latency and reduces the quality of sleep.[9] Caffeine can induce anxiety, particularly at high doses (>200 mg per occasion or >400 mg per day) and in sensitive persons, including those with anxiety or bipolar disorders.[10] There are considerable inter-personal differences in the effects of caffeine owing to differences in receptor distribution and variable metabolism of caffeine among individuals. High caffeine intake causes diuresis, but no detrimental effects on hydration status have been found with a longer-term intake of moderate doses of caffeine (≤400 mg per day).[11]

Cardio-vascular effects

a. Blood pressure: Caffeine intake causes a short-term rise in blood pressure by increasing epinephrine levels. Most people develop tolerance to this effect of caffeine within a week. Chronic caffeine intake results in a modest increase in systolic and diastolic blood pressure.[12,13] Caffeinated coffee contains compounds such as chlorogenic acid, which counteract the blood pressure-raising effect of caffeine.[14]

b. Effects on cholesterol levels: Caffeine is devoid of cholesterol-raising effects. The rise in cholesterol seen with unfiltered coffee can be attributed to another compound, cafestol, found abundantly in unfiltered coffee. In contrast, filtered coffee does not increase serum cholesterol levels.[15]

c. Effects on heart rate and rhythm: There is no association of caffeine intake with atrial or ventricular arrhythmias.[16] Current evidence suggests a protective role of coffee consumption in coronary artery disease, stroke, and death from cardio-vascular causes in the general population or among persons with a history of hypertension, diabetes, or cardio-vascular diseases. The lowest risk is observed with consumption of 3 to 5 standard cups per day.[17]

Respiratory effects

a. Caffeine stimulates the respiratory centre and hence is used in apnoea of pre-maturity.

b. Caffeine also improves airway functions in asthma, increasing the forced expiratory volume (FEV1) by 5% to 18%, with this effect lasting for up to 4 hours.[18]

Endocrine effects

a. Effects on basal metabolic rate: Caffeine reduces appetite, increases the basal metabolic rate, and increases the food-induced thermogenesis by stimulating the sympathetic nervous system and uncoupling of protein-1 expression in brown adipose tissue.[19] Caffeine intake of 6 doses of 100 mg of caffeine can cause a 5% increase in 24-hour energy expenditure.[20] Caffeine intake is associated with slightly less long-term weight gain in cohort studies.[21]

b. Effects on Insulin sensitivity: Caffeine can reduce insulin sensitivity in humans in the short term (15% reduction after a dose of 3 mg caffeine per kilogram of body weight). It indicates an inhibitory effect of caffeine on the storage of glucose as glycogen in muscle and may result from increased epinephrine release.[22] However, consumption of caffeinated coffee does not affect insulin resistance, probably because of the development of tolerance to this side effect of caffeine, or it is offset by longer-term beneficial effects of noncaffeine coffee components.[23]

Others

Prospective cohort studies in the United States, Europe, and Asia have shown a strong inverse association between caffeine intake and the risk of Parkinson's disease. In animal studies, caffeine prevents Parkinson's disease by inhibiting nigrostriatal dopaminergic neurotoxic effects and neurodegeneration through adenosine A2A receptor antagonism.[24]

Coffee and caffeine consumption have also been associated with reduced risks of depression and suicide in several cohorts in the United States and Europe, although these findings may not hold in persons who have very high intakes.[25,26]

Caffeine intake may reduce the risk of gallstone formation by inhibiting the absorption of gallbladder fluid, increasing cholecystokinin secretion, and stimulating gallbladder contraction.[27]

Caffeine and its anaesthetic implications

Use of caffeine for the acceleration of recovery from anaesthesia and post-operative sedation

Most of the anaesthetic agents are believed to act, at least in part by inhibiting the release of neurotransmitters such as glutamate, via presynaptic sites of action.[28] Caffeine is hypothesised to accelerate recovery from general anaesthesia by blocking the adenosine receptors.[29]

Adenosine, a neuromodulator generated by the metabolism of adenosine triphosphate (ATP), plays an important role in sleep homeostasis. Its receptors, namely, A_1 receptors, are widely expressed in the cortex, hippocampus, and cerebellum, and A_{2A} receptors are found primarily in the striatum, nucleus accumbens, and olfactory bulb. Caffeine is an antagonist of both A_1 and A_{2A} receptors, and it has been shown to promote wakefulness in A_1 knockout mice but not A_{2A} knockout mice, suggesting that the arousal-promoting actions of caffeine are primarily mediated by A_{2A} receptors.[30] Adenosine inhibits neurotransmitter release via several mechanisms, and it has also been shown that adenosine more potently inhibits the release of excitatory neurotransmitters than that of their inhibitory counterparts. Additionally, caffeine increases intra-cellular cAMP by inhibiting phosphodiesterase and increased levels of intra-cellular cAMP are known to facilitate neurotransmitter release. There is also evidence that caffeine increases the turnover of several monoamine transmitters such as dopamine, noradrenaline, and 5-hydroxy tryptamine, which produce central nervous system (CNS) stimulatory effects.[31,32]

In current anaesthesia practice, recovery from anaesthesia is governed by passive clearance of the anaesthetic agent after its discontinuation and there is no pharmacological agent anaesthesia proven for active reversal of general anaesthesia. Agents for active reversal of general anaesthesia may hasten recovery and may be useful for treating delayed emergence, emergence delirium, and post-operative cognitive dysfunction anaesthesia, which may allow for early discharge, better outcomes, and lower costs. Current evidence suggests that caffeine may enhance the speed of recovery, although prospective human trials are required for optimal dosing and timing of administration.[33–35]

Fong *et al.* found that caffeine accelerated the emergence from isoflurane anaesthesia in humans, even when isoflurane was used in higher concentrations. They also found that preladenant (selective A_{2a} adenosine receptor antagonist) and forskolin (([cAMP] i) elevating drug) accelerated recovery from anaesthesia and their combination had an additive effect which was as effective as caffeine. This suggests that both A_{2A} receptor blockade and $[cAMP]_i$ elevation play a role in caffeine's ability to accelerate emergence from anaesthesia.[33]

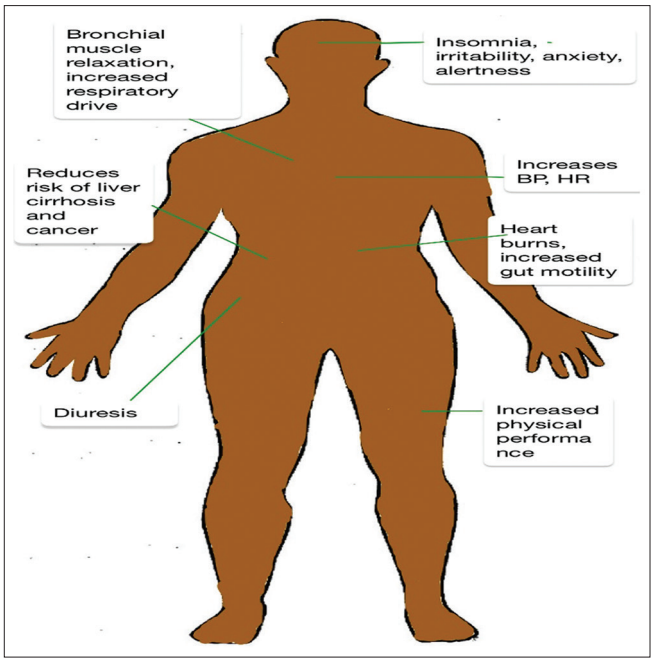

Figure 2: Diagrammatic representation of effects of caffeine on all organ systems

Animal studies have found that adenosine decreases arousal by reducing cholinergic neurotransmission and that adenosine build-up in the brain during prolonged wakefulness can increase sensitivity to anaesthetic-induced hypnosis. Consistent with this notion, sleep deprivation decreases the dose requirement for loss of consciousness by anaesthetics in rats, and this effect is partially reversed by A_1 and A_{2A} antagonists.[36] Caffeine has also been shown to increase the local release of acetylcholine in the prefrontal cortex. A double-blind crossover study showed that caffeine accelerates the emergence from isoflurane anaesthesia in healthy human volunteers.[33] Taken together, these findings are suggestive that anaesthetics partially converge onto adenosine-mediated sleep pathways to produce unconsciousness, and inhibition of A_1 and A_{2A} adenosine receptors with drugs such as caffeine appears to be an effective strategy for promoting emergence from general anaesthesia [Table 2].[33,35,37–40]

Treatment of children with post-sedation paradoxical hyper-activity

Because of extensive overlapping of symptoms of post-sedation paradoxical hyper-activity with attention deficit hyper-activity disorder (ADHD), stimulant drugs have been tried to manage this condition. Administration of stimulant drugs such as caffeine and amphetamines has been shown to improve concentration and control in hyper-active children.[41] Bunt and Towbin concluded that oral caffeine can be used as a treatment modality for paradoxical hyper-activity.[42] The precise mechanism of action of stimulants is still unclear, but it has been suggested that their effects on hyper-activity are produced by their stimulant action on dopaminergic and noradrenergic

Table 2: Role of caffeine in awakening from anaesthesia

Author name	Study type	Procedure	Intervention	Control	Outcome	Result
Robert fang *et al.*[33]	Human RCT double blind crossover study, n=8	Healthy male volunteers anaesthetised with Isoflurane 1.2% for 1 hr. During the last 10 mins, patients received either the study drug or placebo. The primary outcome was the average difference in time to emergence after isoflurane discontinuation between caffeine and saline sessions. Secondary outcomes included the end-tidal isoflurane concentration at emergence, vital signs, and bispectral index values measured throughout anaesthesia and emergence.	caffeine citrate (15 mg/kg, equivalent to 7.5 mg/kg of caffeine base)	saline	Mean time to emergence-Saline-16.5 +- 3.9 min. Caffeine - 9.6+-5.1 with a difference of 6.9 mins (P=0. 002). Participants emerged at a higher expired isoflurane concentration, manifested more rapid return to baseline bispectral index values, and were able to participate in psychomotor testing sooner when receiving caffeine.	Favours caffeine use for awakening from anaesthesia
N. Gouda *et al.*[35]	Human study, randomised double- blinded placebo-controlled trial, N=60	OSA pts for UPPP (uvulopalatopharyngopl) under GA. Induced with fentanyl, propofol, and atracurium and maintained with Sevo 2.5-3% in 100% O_2. After surgery and discontinuation of sevo, patients were administered the control or study drug. BIS, HR. Time to recovery (eye opening, extubation, response to verbal command, duration of recovery, duration of PACU stay) and post-extubation respiratory complications (laryngospasm, supraglottic obstruction, reintubation, breath hold, desaturation<95%) were noted.	Caffeine 500 mg	saline	Time to eye opening, extubation, response to verbal commands and duration of recovery, and duration of PACU stay were significantly shorter in the caffeine group P<0.05. The BIS values were significantly higher in the caffeine group from minute 3 to minute 11 compared to the placebo. P<0.05. The number of patients who developed adverse post-extubation events during the recovery period and in the PACU was significantly less in the caffeine group compared to the placebo P<0.05.	Favours caffeine
Emami S *et al.*[37]	Human study, RCT (n=18)	Patients undergoing inguinal herniorrhaphy under GA were randomised to receive either study drugs or placebo. The primary outcome was laryngeal mask airway (LMA) removal time at the end of anaesthesia. Intra-operative haemodynamic data and side effects such as nausea, vomiting, dysrhythmia, cyanosis, and seizures in the recovery room were also recorded.	Caffeine 10 mg/kg IV	saline	Time from the induction of anaesthesia to LMA removal was 44.77±7.87 min in the placebo group and 44.55±10.68 min in the caffeine group. There was no significant difference between the two groups (P=0.961).	Does not favour caffeine
Zoreh Sadat *et al.*[38]	Human study, double-blinded randomised control trial (n=80)	Mechanically ventilated ICU patients were randomly allocated into two groups (intervention and control). Drugs were administered through a nasogastric tube 30 min after breakfast. Respiratory parameters were recorded and compared in the two groups 2 minutes before the intervention and 30 minutes and 60 minutes after the intervention.	3.5 grams of espresso in 100 ml of water	100 ml of distilled water	Spontaneous respiratory rate, tidal volume, the minute ventilation rate, and arterial O_2 saturation increased in the intervention group compared to the control group, but the increase was statistically significant only for the spontaneous respiratory rate and tidal volume.	Favours caffeine

Contd...

Table 2: Contd...

Author name	Study type	Procedure	Intervention	Control	Outcome	Result
Michael evan *et al.*[39]	Case report	A 16-year-old case of trisomy 10 with history of OSA, delayed emergence, and post-operative hypopnoea with impacted teeth came for dental extraction under GA. After extubation in the recovery room, the patient had frequent episodes of desaturation and hypopnoea that required continued re-assessments by an anaesthesiologist. Over time, the patient's alertness decreased secondary to his hypo-ventilation.	Caffeine citrate 60 mg IV administered over 10 min	-	Within 15 minutes of administration, the patient's alertness and O_2 saturations improved. Respirations were no longer shallow. His blood pressure and heart rate remained stable. After 85 minutes, the patient was discharged in stable conditions, with no further oxygen desaturations after the administration of caffeine.	Favours caffeine
Nafisseh S Warner *et al.*[40]	Human retrospective study, n=151	Heavily sedated patients in PACU were administered caffeine and changes in RASS, RR, and SpO_2 during 90 minutes period prior to and following intervention were noted. Generalized estimating equations (GEEs) with explanatory variables of time, caffeine, and the time-by-caffeine interaction were created to assess changes in the variables of interest after caffeine administration.	After administration of caffeine (125-250 mg), median dose 150	Before caffeine administration	Following the caffeine administration, RASS scores were significantly increased (estimate=0.57, SE=0.14, P<0.001), with no evidence of a change in the slope (interaction effect = −0.0003, SE=0.004, P=0.93). No meaningful improvement in RR or oxyHb saturation.	Favours caffeine

Table 3: Role of caffeine in paradoxical hyper-activity

Author	Study: article/ human/animal	Procedure	Intervention	Control	Outcome	Results
Christopher Bunt *et al.*[42]	Human study, case series (n=25)	Children undergoing radiological imaging under sedation with pentobarbital (4.36 mg/kg) who developed paradoxical hyper-activity were given caffeine.	8.6 mg/kg caffeine in the form of mountain dew	-	24 among the patients calmed down within 10–90 mins of ingestion	Favours caffeine
Joan T Rubin *et al.*[44]	Human	360 children diagnosed with post-sedation paradoxical hyper-activity (PH) following radiological procedures.	Iv group (n=131): 20 mg/kg caffeine citrate (to a maximum of 200 mg) Oral group (n=88) - 1.0-2.5 mg/kg caffeine (in marketed drinks)	No intervention	The untreated control group required a significantly longer time to recover (P<0.01) than IV caffeine 20 mg/kg group but not a significantly longer time than oral caffeine 1-2.5 mg/kg group.	Favours IV caffeine

pathways,[43] which in the case of caffeine is mediated by its antagonistic action on adenosine receptors [Table 3].[44]

Caffeine for Post-operative bowel paralysis

Some studies have demonstrated the efficacy of caffeine in increasing bowel motility and its use for preventing post-operative bowel paralysis.[45–49] However, none of the studies was able to conclude much about the mechanism by which caffeine exerts this effect. Some researchers have hypothesised the role of neural and neurohumoral mechanisms such as cholecystokinin or gastrin secretion and the role of intestinal secretions (because caffeine stimulates intestinal secretions) as the mechanisms by which caffeine increases intestinal/colonic motility.[50,51] Another study found that caffeine induced contractions in *in vitro* guinea pig taenia coli by releasing calcium ions from their intra-cellular binding sites.[52]

Most studies have tried to find a correlation between caffeine intake and post-operative ileus using caffeinated and de-caffeinated coffee as interventional groups and found a positive correlation, but the degree of correlation is higher with caffeinated groups than with the de-caffeinated coffee.[53,54] However, another study found de-caffeinated coffee to be

Table 4: Role of caffeine in bowel paralysis

Author	Study: article/ human/animal	Procedure	Intervention	Control	Outcome	Results
Gkegkes I.D *et al.*[45]	Human study, Meta-analysis of four studies (n=341)	Pub-med, SCOPUS, and Cochrane register were systematically searched; outcomes analysed were time to first bowel movement, time to flatulence, time to tolerance of solid diet, additional use of laxatives, need for re-insertion of nasogastric tube, and need for re-surgery.			Post-operative caffeine use reduces time to first bowel movement, time to flatulence, and time to tolerance of solid diet	Favours caffeine
SA Müller *et al.*[46]	Multi-centre open label randomised trial (n=80)	Patients undergoing elective open or laparoscopic colectomy were assigned randomly before surgery to receive either study drugs or the control drug. The primary endpoint was time to first bowel movement; secondary endpoints were time to first flatus, time to tolerance of solid food, length of hospital stay, and peri-operative morbidity.	100 ml of caffeine	100 ml of water	In ITT analysis, the time to the first bowel movement was significantly shorter in the coffee arm than in the water arm with a mean±SD of 60·4±21·3 hrs versus 74.0±21.6 hrs; P=0·006).	Favours caffeine
Kemal Gungorduk *et al.*[48]	Human study, RCT (n=114)	Patients undergoing TAH and bilateral salphingo-oophorectomy with pelvic and paraaortic lymphadenectomy for gynaecological malignancies were given study drug vs standard of care. The primary outcome was time to first passage of flatus. Secondary outcomes were time to first defecation, time to first bowel movement, and time to tolerance of solid diet.	Thrice daily consumption of coffee	Standard of care	Mean time to flatus–30.2±8.0 vs 40.2±12.1 hours, P<0.00. Mean time to ability to tolerate food and mean time to defecation were reduced significantly.	Favours caffeine
Christina Kruse *et al.*[56]	Human study, RCT, double-blinded (n=180)	Patients undergoing laparoscopic colectomy or upper rectum resection randomised to receive the study drug or control starting with POD1. Drug capsules will be loaded with a radio-opaque marker to assess colonic passage time (primary objective) by abdominal X-ray. Secondary objectives are post-operative morbidity and mortality, sleeping behaviour, and length of hospital stay.	Group 1 (n=60)- Caffeine 100 mg TDS Group 2 (n=60)- Caffeine 300 mg TDS	Placebo (corn-starch)	Ongoing trial	-

Table 5: Role of caffeine in apnoea and obstructive sleep apnoea

Author	Study: article/ human/animal	Procedure	Intervention	Control	Outcome	Results
Khalil S N *et al.*[58]	Human study, RCT double-blinded (n=72)	Children with OSA scheduled for adenotonsillectomy received GA and the study drug. The primary outcome evaluated the number of children who developed adverse post-extubation respiratory events, and the secondary outcome was the incidence of adverse post-extubation respiratory events.	20 mg/kg IV caffeine	saline	The overall incidence of adverse post-operative respiratory events was less in the caffeine group than in the placebo group (P=0.0196).	Favours caffeine
Anwar M *et al.*[61]	Human study, case series (n=23)	In patients with apnoea of pre-maturity, after 12 hours of pneumogram, patients were administered caffeine. Repeat pneumogram done after 7-10 days	20 mg/kg loading dose followed by 5 mg/kg OD		All patients showed disappearance of prolonged apnoea	Favours caffeine
Leila G Wellborn *et al.*[62]	Human study, double-blinded, RCT (n=20)	Pre-mature infants born <37 weeks with conceptional age <44 weeks undergoing inguinal hernia repair under GA were randomised between study drug and control group. Post-operative incidence of apnoea and prolonged apnoea were measured	5 mg IV caffeine (n=9)	Saline (n=11)	None of the patients in caffeine group developed prolonged apnoea, whereas 8% patients experience them in saline group, P<0.002	Favours caffeine

more effective in the treatment of ileus than caffeinated coffee[44,46,48,55,56] [Table 4]. Further RCTs are required using caffeine as the sole drug in the intervention arm to establish its role in paralytic ileus.

Table 6: Role of caffeine in post-dural puncture headache

Author	Study: article/ human/animal	Procedure	Intervention	Control	Outcome	Results
Esmaoglu *et al.*[67]	Human study, prospective RCT (n=210)	Patients undergoing surgery under spinal anaesthesia were divided into three groups with n=70. Patient interview conducted on days 1, 2, 3, 4, and 7 regarding incidence of PDPH and side effects like lack of sleep, tachycardia, and hypertension	Group 2 received 500 mg of paracetamol +75 mg of caffeine orally. Group 3 received 500 mg of paracetamol +125 mg of caffeine. All patients received the drug thrice daily	Group 1: placebo	No difference in incidence of PDPH between the three groups, 15.7% in Group 1, 14.28% in Group 2, and 14.28% in Group 3, P>0.05	No role of caffeine in prophylaxis for PDPH
Camann *et al.*[68]	Human study, double-blinded, placebo-controlled trial (n=40)	Patients with PDPH were randomised to receive either the study drug or control drug. VAS scores were assessed before drug, 4 and 24 hours later.	Oral caffeine 300 mg	placebo	Delta VAS (initial VAS – VAS at 4 hours) was significantly better in caffeine group (90%) compared to placebo group (60%), P – 0.014	Favours caffeine
D D Erol *et al.*[69]	Human study, prospective RCT (n=42)	Patients suffering from PDPH were given gabapentin or caffeine+ergotamine. Patients were asked to record the severity of their headache and the number of vomiting episodes on a visual analogue scale (VAS) on days 1, 2, 3, and 4.	gabapentin	Caffeine + ergotamine	Gabapentin group had less pain, nausea, and vomiting compared to the caffeine + ergotamine group.	Does not favour caffeine
A Yücel *et al.*[70]	Human study, randomised double-blinded placebo-controlled trial	Patients undergoing lower abdominal or lower extremity surgery were randomised to receive either the study drug or placebo. VAS and analgesic demand were compared between the two groups.	1000 ml of saline with 500 mg of caffeine	1000 ml of normal saline	VAS score was significantly lower in the study group compared to the control group with lesser analgesic demand	Favours caffeine
Zeger *et al.*[71]	Human study, prospective double-blinded RCT, n=37	Patients with post-dural puncture headache were randomised to receive either the study drug or control drug. Values on a 100-mm visual analogue scale (VAS) were recorded at 0, 60, and 120 minutes to assess pain.	IV cosyntropin	IV caffeine	Analysis was based on intention to treat. Caffeine was 80% (95% CI 60-100%) effective, and cosyntropin was 56% (95% CI 33-79%) effective in treating post-dural puncture headaches. The group's VAS scores at 0, 60, and 120 minutes were 80 mm, 41 mm, and 31 mm for caffeine and 80 mm, 40 mm, and 33 mm for cosyntropin, respectively (P=0.66)	Favours caffeine
Sechzer *et al.*[72]	Human study, double-blinded study, n=41	Patients with PDPH were randomized to receive either the study drug or placebo. Those patients who did not obtain relief with the first treatment were given 500 mg of caffeine IV.	Caffeine sodium benzoate 0.5 g/2 ml	saline	In all, 27 of 38 patients given 500 mg to 1 g of I obtained relief, while only 3 of 21 given II obtained relief.	Favours caffeine

Use of Caffeine in the prevention of Neonatal Apnoea and treatment of Obstructive Sleep Apnoea (OSA) in Children

The pathophysiology of OSA is multi-factorial, and both anatomical and neuromuscular abnormalities are known to contribute to its pathogenesis. It has been postulated that a central element may also contribute to OSA.[57,58]

Several mechanisms have been suggested about how caffeine is useful in managing OSA. Caffeine is a cardiac and central nervous system stimulant owing to its antagonistic action on adenosine receptors. Caffeine increases the central respiratory drive and increases the sensitivity of the chemoreceptors to carbon dioxide.[59] Other suggested mechanisms include potentiation of catecholamine action and increased inspiratory muscle endurance.[60,61] By these mechanisms, caffeine increases ventilation and decreases the episodes of hypoxia in subjects with OSA [Table 5].[58,61,62]

Caffeine in PDPH

The exact pathophysiology of PDPH is not clearly understood. However, some researchers believe that loss of cerebrospinal fluid (CSF) from the dural puncture site leads to loss of cushioning effect of CSF, leading to headache.[63] It has also been suggested that a sudden decrease in CSF pressure causes an increase in the perfusion of the brain as the blood vessels dilate to compensate for the decrease in CSF volume, causing pain similar to vascular headache.[64] Caffeine augments the CSF production by stimulating the sodium–potassium pumps and also causes cerebral vasoconstriction because of its antagonistic effects on adenosine receptors.[65,66] Table 6 summarises current evidence about the role of caffeine in PDPH.[67–72]

Conclusion

Caffeine exerts a multitude of effects on diverse organ systems, and apart from recreational usage, it has been used as a principal treatment modality routinely used for PDPH and apnoea of pre-maturity. The search for novel drugs needed for the reversal of anaesthesia has provoked newer interests in drugs such as caffeine. Though more conclusive evidence from RCTs is needed for a routine recommendation, the available evidence shows the feasibility of its use for reversing anaesthesia. Further studies should also investigate the potential therapeutic utility of caffeine in post-operative bowel paralysis, where the available evidence suggests the possible role of caffeine in early bowel rehabilitation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. WHO Model List of Essential Medicines 18th list (April 2013). Available from: https://apps.who.int/iris/bitstream/handle/10665/93142/EML_18_eng.pdf. [Last accessed on 2022 Aug 01].
2. Heckman MA, Weil J, de Mejia EG. Caffeine (1, 3, 7-trimethylxanthine) in foods: A comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci 2010;75:R77–87.
3. Nehlig A. Interindividual differences in caffeine metabolism and factors driving caffeine consumption. Pharmacol Rev 2018;70:384–411.
4. Rybak ME, Sternberg MR, Pao CI, Ahluwalia N, Pfeiffer CM. Urine excretion of caffeine and select caffeine metabolites is common in the US population and associated with caffeine intake. J Nutr 2015;145:766–74.
5. Institute of Medicine (US) Committee on Military Nutrition Research. Caffeine for the Sustainment of Mental Task Performance: Formulations for Military Operations. Washington (DC): National Academies Press (US); 2001. 2, Pharmacology of Caffeine. Available from: https://www.ncbi.nlm.nih.gov/books/NBK223808/. [Last accessed on 2022 Aug 01].
6. Ribeiro JA, Sebastião AM. Caffeine and Adenosine. J Alzheimer's Dis 2010;20:S3–15.
7. McLellan TM, Caldwell JA, Lieberman HR. A review of caffeine's effects on cognitive, physical and occupational performance. Neurosci Biobehav Rev 2016;71:294–312.
8. Derry CJ, Derry S, Moore RA. Caffeine is an analgesic adjuvant for acute pain in adults. Cochrane Database Syst Rev 2014;12:CD009281.
9. Clark I, Landolt HP. Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials. Sleep Med Rev 2017;31:70–8.
10. Lara DR. Caffeine, mental health, and psychiatric disorders. J Alzheimers Dis 2010;20:S239–48.
11. Armstrong LE, Pumerantz AC, Roti MW, Judelson DA, Watson G, Dias JC, *et al*. Fluid, electrolyte, and renal indices of hydration during 11 days of controlled caffeine consumption. Int J Sport Nutr Exerc Metab 2005;15:252-65.
12. Noordzij M, Uiterwaal CSPM, Arends LR, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to chronic intake of coffee and caffeine: A meta-analysis of randomized controlled trials. J Hypertens 2005;23:921-8.
13. Steffen M, Kuhle C, Hensrud D, Erwin PJ, Murad MH. The effect of coffee consumption on blood pressure and the development of hypertension: A systematic review and meta-analysis. J Hypertens 2012;30:2245-54.
14. Mesas AE, Leon-Muñoz LM, Rodriguez-Artalejo F, Lopez-Garcia E. The effect of coffee on blood pressure and cardiovascular disease in hypertensive individuals: A systematic review and meta-analysis. Am J Clin Nutr 2011;94:1113-26.
15. Jee SH, He J, Appel LJ, Whelton PK, Suh II, Klag MJ. Coffee consumption and serum lipids: A meta-analysis of randomized controlled clinical trials. Am J Epidemiol 2001;153:353-62.
16. Zuchinali P, Ribeiro PAB, Pimentel M, da Rosa PR, Zimerman LI, Rohde LE. Effect of caffeine on ventricular arrhythmia: A systematic review and meta-analysis of experimental and clinical studies. Europace 2016;18:257-66.
17. Ding M, Bhupathiraju SN, Satija A, van Dam RM, Hu FB. Long-term coffee consumption and risk of cardiovascular disease. Circulation 2014;129:643-59.
18. Welsh EJ, Bara A, Barley E, Cates CJ. Caffeine for asthma. Cochrane Database Syst Rev 2010;2010:CD001112.
19. Harpaz E, Tamir S, Weinstein A, Weinstein Y. The effect of caffeine on energy balance. J Basic Clin Physiol Pharmacol 2017;28:1-10.
20. Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: Influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. Am J Clin Nutr 1989;49:44-50.
21. Lopez-Garcia E, van Dam RM, Rajpathak S, Willett WC, Manson JE,

Hu FB. Changes in caffeine intake and long-term weight change in men and women. Am J Clin Nutr 2006;83:674-80.
22. Keijzers GB, de Galan BE, Tack CJ, Smits P. Caffeine can decrease insulin sensitivity in humans. Diabetes Care 2002;25:364-9.
23. Wedick NM, Brennan AM, Sun Q, Hu FB, Mantzoros CS, van Dam RM. Effects of caffeinated and decaffeinated coffee on biological risk factors for type 2 diabetes: A randomized controlled trial. Nutr J 2011;10:1–9.
24. Xu K, di Luca DG, Orrú M, Xu Y, Chen JF, Schwarzschild MA. Neuroprotection by caffeine in the MPTP model of Parkinson's disease and its dependence on adenosine A2A receptors. Neuroscience 2016;322:129–37.
25. Lucas M, O'Reilly EJ, Pan A, Mirzaei F, Willett WC, Okereke OI, *et al*. Coffee, caffeine, and risk of completed suicide: Results from three prospective cohorts of American adults. World J Biol Psychiatry 2014;15:377-86.
26. Tanskanen A, Tuomilehto J, Viinamäki H, Vartiainen E, Lehtonen J, Puska P. Heavy coffee drinking and the risk of suicide. Eur J Epidemiol 2000;16:789–91.
27. Lillemoe KD, Magnuson TH, High RC, Peoples GE, Pitt HA. Caffeine prevents cholesterol gallstone formation. Surgery 1989;106:400-7
28. Wu XS, Sun JY, Evers AS, Crowder M, Wu LG. Isoflurane inhibits transmitter release and the presynaptic action potential. Anesthesiology 2004;100:663–70.
29. Fong R, Khokhar S, Chowdhury AN, Xie KG, Wong JHY, Fox AP, *et al*. Caffeine accelerates recovery from general anesthesia via multiple pathways. J Neurophysiol 2017;118:1591–7.
30. Lazarus M, Shen HY, Cherasse Y, Qu WM, Huang ZL, Bass CE, *et al*. Arousal effect of caffeine depends on adenosine a2a receptors in the shell of the nucleus accumbens. J Neurosci 2011;31:10067–75.
31. Hadfield MG, Milio C. Caffeine and regional brain monoamine utilization in mice. Life Sci 1989;45:2637–44.
32. Fredholm BB. Adenosine, Adenosine Receptors and the Actions of Caffeine. Pharmacol Toxicol 1995;76:93–101.
33. Fong R, Wang L, Zacny JP, Khokhar S, Apfelbaum JL, Fox AP, *et al*. Caffeine accelerates emergence from isoflurane anesthesia in humans: A randomized, double-blind, crossover study. Anesthesiology 2018;129:912–20.
34. Wang Q, Fong R, Mason P, Fox AP, Xie Z. Caffeine accelerates recovery from general anesthesia. J Neurophysiol 2014;111:1331–40.
35. Gouda NM. Intravenous caffeine for adult patients with obstructive sleep apnea undergoing uvulopalatopharyngoplasty: Effects on postoperative respiratory complications and recovery profile. Med J Cairo Univ 2010;78:155-9.
36. Dort CJV, Baghdoyan HA, Lydic R. Adenosine A1 and A2A receptors in mouse prefrontal cortex modulate acetylcholine release and behavioral arousal. J Neurosci 2009;29:871–81.
37. Emami S, Panah A, Hakimi SS, Sahmeddini MA. Effect of caffeine on the acceleration of emergence from general anesthesia with inhalation anesthetics in children undergoing inguinal herniorrhaphy: A randomized clinical trial. Iran J Med Sci 2022;47:107-13.
38. Sadat Z, Salehi N, Afazel MR, Aboutalebi MS, Dianati M. The effect of Espresso coffee consumption through the gastric tube on respiratory indicators among mechanically ventilated patients: A randomized clinical trial. Hayat 2017;23:185-195.
39. Evans M, Lam H, Austin T. Intravenous caffeine rescue for postoperative hypoventilation in a 16-year-old with trisomy 10: A case report. A A Case Rep 2017;9:50–1.
40. Warner NS, Warner MA, Schroeder DR, Sprung J, Weingarten TN. Effects of caffeine administration on sedation and respiratory parameters in patients recovering from anesthesia. Bosn J Basic Med Sci 2018;18:101-4.
41. Schechter MD, Timmons GD. Objectively measured hyperactivity—II. Caffeine and amphetamine effects. J Clin Pharmacol 1985;25:276–80.
42. Bunt C, Towbin R. Treatment of pentobarbital sodium (Nembutal) hyperactivity: A new approach. Pediatr Radiol 2000;30:204.
43. Fox AM, Rieder MJ. Risks and benefits of drugs used in the management of the hyperactive child. Drug Safety 1993;9:38–50.
44. Rubin JT, Towbin RB, Bartko M, Baskin KM, Cahill AM, Kaye RD. Oral and intravenous caffeine for treatment of children with post-sedation paradoxical hyperactivity. Pediatr Radiol 2004;34:980–4.
45. Gkegkes ID, Minis EE, Iavazzo C. Effect of caffeine intake on postoperative ileus: A systematic review and meta-analysis. Dig Surg 2020;37:22–31.
46. Müller SA, Rahbari NN, Schneider F, Warschkow R, Simon T, Frankenberg MV, *et al*. Randomized clinical trial on the effect of coffee on postoperative ileus following elective colectomy. Br J Surg 2012;99:1530–8.
47. Kuo SC, Mu PF, Chang LY, Chou SS, Lee MY, Su JY, *et al*. Effectiveness of coffee for postoperative ileus in patients following abdominal surgery: A systematic review protocol. JBI Database System Rev Implement Rep 2018;16:2072–9.
48. Güngördük K, Özdemir İA, Güngördük Ö, Gülseren V, Gokçü M, Sancı M. Effects of coffee consumption on gut recovery after surgery of gynaecological cancer patients: A randomized controlled trial. Am J Obstet Gynecol 2017;216:145e1-7.
49. Ziouziou I, Ammani A, Karmouni T, el Khader K, Koutani A, Iben Attya Andaloussi A. Does chewing gum improve postoperative results in patients undergoing radical cystectomy? A systematic review of literature and meta-analysis. ProgrUrol 2017;27:513–20.
50. Snape WJ, Matarazzo SA, Cohen S. Effect of eating and gastrointestinal hormones on human colonic myoelectrical and motor activity. Gastroenterology 1978;75:373–8.
51. Wald A, Back C, Bayless TM. Effect of caffeine on the human small intestine. Gastroenterology 1976;71:738–42.
52. Obara K, Yabu H. Effects of caffeine on contraction and chlorotetracycline fluorescence in isolated single smooth muscle cells of guinea pig taenia coli. Jpn J Physiol 1982;32:1003–6.
53. Brown SR, Cann PA, Read NW. Effect of coffee on distal colon function. Gut 1990;31:450–3.
54. Rao SSC, Welcher K, Zimmerman B, Stumbo P. Is coffee a colonie stimulant? Eur J Gastroenterol Hepatol 1998;10:113-8.
55. Dulskas A, Klimovskij M, Vitkauskiene M, Samalavicius NE. Effect of coffee on the length of postoperative ileus after elective laparoscopic left-sided colectomy: A randomized, prospective single-center study. Dis Colon Rectum 2015;58:1064–9.
56. Kruse C, Müller SA, Warschkow R, Lüthi C, Brunner W, Marti L, *et al*. Does caffeine reduce postoperative bowel paralysis after elective laparoscopic colectomy? (CaCo trial): Study protocol for a randomized controlled trial. Trials 2016;17:1–9.
57. Marcus CL. Pathophysiology of childhood obstructive sleep apnea: Current concepts. Respir Physiol 2000;119:143–54.
58. Khalil SN, Maposa D, Ghelber O, Rabb MF, Matuszczak M, Ganesan BA, *et al*. Caffeine in children with obstructive sleep apnea. Middle East J Anaesthesiol 2008;19:885–99.
59. Aranda JV, Turmen T. Methylxanthines in apnea of prematurity. Clin Perinatol 1979;6:87–108.
60. Aubier M, Murciano D, Viires N, Lecocguic Y, Pariente R. Diaphragmatic contractility enhanced by aminophylline: Role of extracellular calcium. J Appl Physiol Respir Environ Exerc Physiol 1983;54:460–4.
61. Anwar M, Mondestin H, Mojica N, Novo R, Graff M, Hiatt M, *et al*. Effect of caffeine on pneumogram and apnoea of infancy. Arch Dis Child 1986;61:891–5.
62. Welborn LG, de Soto H, Hannallah RS, Fink R, Boeckx R. The use

of caffeine in the prevention of postanesthetic apnea in premature infants. Anesthesiology 1987;67:A507.
63. Morewood GH. A rational approach to the cause, prevention and treatment of post-dural puncture headache. CMAJ 1993;149:1087–93.
64. Grant R, Condon B, Hart I, Teasdale GM. Changes in intracranial CSF volume after lumbar puncture and their relationship to post-LP headache. J Neurol Neurosurg Psychiatry 1991;54:440–2.
65. Straube A, Neudert C, Glas M, Brüning R, Padovan CS. The so-called spontaneous low CSF pressure syndrome. Case results indicating a disturbance in CSF/blood volume regulation]. Nervenarzt 2004;75:1194–9.
66. Mathew RJ, Wilson WH. Caffeine-induced changes in the cerebral circulation. Stroke 1985;16:814–7.
67. Esmaoglu A, Akpinar H, Uğur F. Oral multidose caffeine-paracetamol combination is not effective for the prophylaxis of post-dural puncture headache. J Clin Anesth 2005;17:58–61.
68. Camann WR, Murray RS, Mushlin PS, Lambert DH. Effects of oral caffeine on postdural puncture headache. A double-blind, placebo-controlled trial. Anesth Analg 1990;70:181-4.
69. Erol DD. The analgesic and antiemetic efficacy of gabapentin or ergotamine/caffeine for the treatment of post-dural puncture headache. Adv Med Sci 2011;56:25–9.
70. Yücel A, Ozyalçin S, Talu GK, Yücel EC, Erdine S. Intravenous administration of caffeine sodium benzoate for post-dural puncture headache. Reg Anesth Pain Med. 1999;24:51–4.
71. Zeger W, Younggren B, Smith L. Comparison of cosyntropin versus caffeine for post-dural puncture headaches: A randomized double-blind trial. World J Emerg Med 2012;3:182-5.
72. Sechzer PH, Abel L. Post-spinal anesthesia headache treated with caffeine. Evaluation with demand method. Part I. Curr Ther Res Clin Exp 1978;24:307-12.