Use of Therapeutic Caffeine in Acute Care Post-operative and Critical Care Settings: a Scoping Review

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Abstract

Background

Caffeine is the most utilised psychoactive drug worldwide. However, caffeine withdrawal and the therapeutic use of caffeine in intensive care and in the peri-operative period have not been well summarised. Our objective was to conduct a scoping review of caffeine withdrawal and use in the intensive care unit (ICU) and post-operative patients.

Methods

PubMed, Embase, CINAHL Complete, Scopus and Web of Science were systematically searched for studies investigating the effects of caffeine withdrawal or administration in ICU patients and in the peri-operative period. Areas of recent systematic review such as pain or post-dural puncture headache were not included in this review. Studies were limited to adults.

Results

Of 2268 articles screened, 26 were included and grouped into two themes of caffeine use in the peri-operative period and in the ICU. Caffeine withdrawal in the post-operative period increases the incidence of headache, which can be effectively treated prophylactically with peri-operative caffeine. There were no studies investigating caffeine withdrawal or effect on sleep wake cycles, daytime somnolence, or delirium in the intensive care setting. Administration of caffeine results in faster emergence from sedation and anaesthesia, particularly in individuals who are at high risk of post-extubation complications. There has only been one study investigating caffeine administration to facilitate post-anaesthetic emergence in ICU. Caffeine administration appears to be safe in moderate doses in the peri-operative period and in the intensive care setting.

Conclusions

Although caffeine is widely used, there is a paucity of studies investigating withdrawal or therapeutic effects in patients admitted to ICU and further novel studies are a priority.

Background

Caffeine is the most widely used psychoactive drugs worldwide and has been used therapeutically in anaesthesia, critical care, and pain medicine. Peri-operatively, caffeine (≥ 100 mg) provides adjunctive pain relief effects when added to common analgesics, and is commonly used in the treatment of post-dural puncture headaches. Post-operatively the use of caffeine after elective colorectal surgery has been recommended to reduce the incidence of post-operative ileus. Caffeine has been used in neonatal intensive care units (ICU) to treat apnoea related syndromes with no long-term adverse effects.
However, its effects are less well defined in critically ill adults and therapeutic use must be considered in the context of whether patients are chronic users or not.

Caffeine is a derivative of methylxanthine that acts by inhibiting adenosine receptors and the downstream neurotransmitters, promoting lipolysis and can increase blood catecholamines\textsuperscript{7, 8}. In infants, caffeine and methylxanthine act on central and peripheral receptors that stimulate the medullary respiratory centre\textsuperscript{9}. This has a range of physiologic, cognitive, and psychomotor effects and influences wakefulness and sleep\textsuperscript{10–12}. Caffeine has a complex relationship with endothelial cell function in which it can cause vasodilation by increased intracellular calcium increasing nitric oxide, or vasoconstriction mediated by adenosine antagonism. The effects on the cardiovascular system are seen by mild changes to heart rate and blood pressure, with no consensus in the literature that increased caffeine consumption will increase risk of arrhythmias\textsuperscript{13–16}. Abrupt cessation of caffeine in chronic users, such as with fasted patients post-operatively, will affect 10–55\% of individuals and may have adverse effects such as increased cerebral blood flow velocity, quantitative electroencephalogram changes and symptoms including headache, drowsiness, decreased alertness, flu-like symptoms, nausea/vomiting, and myalgias\textsuperscript{17, 18}. Its potential uses to treat withdrawal symptoms, to moderate disturbed sleep-wake cycles, and reduce ICU/post-operative delirium have not been systematically reviewed. Our objective was to conduct a scoping review surrounding the use of caffeine in acute care post-operative and critical care settings in order to summarize the available published evidence and to identify future research priorities.

**Methods**

**Data sources**

PubMed, Embase, CINAHL Complete, Scopus and Web of Science were searched using the Medical Subject Headings (MeSH) and key words on 1st May 2020 (see appendix 1).

**Study questions**

1. What is the evidence for caffeine in the ICU and what is the evidence for caffeine peri-operatively?

   a. Caffeine withdrawal and administration on the development of post-operative headache or delirium

   b. Caffeine withdrawal and administration on induction and emergence from sedation

   c. Safety and changes associated with caffeine administration

**Inclusion criteria**

Studies of any methodology were included if they investigated the effect or safety of caffeine or caffeine-containing products on hospitalised patients, with a focus on peri-operative patients and those admitted to the ICU.
Exclusion criteria

Studies were excluded if they specifically evaluated post-dural puncture headaches, caffeine as a pain adjunct, effect on ileus or gastrointestinal motility, the risk of arrhythmias from habitual caffeine intake, effects during pregnancy, or were community-based. Studies were also excluded if they investigated the effect of caffeine outside of the intensive care or post-operative hospital setting. Studies that reported on caffeine overdose in the community were not included. Studies were excluded if they reported on individuals under 18 years of age. Animal studies, review articles and editorials that did not contain novel information were excluded.

Study protocol

The review methodology was conducted according to the Joanna Briggs Institute 19. Study selection was performed independently by two physician reviewers (MB, VR) at each stage 1 (title and abstract) and stage 2 (full text screening). Any discrepancy was solved by a discussion between the two reviewers and if needed a third reviewer (KL) was available to make the final decision.

Once all articles for inclusion were screened, data was extracted by one of the authors (MB) using the data extraction table. When any information included in a study was unclear, the authors were contacted to provide clarification or further details.

Analysis

Analysis was primarily descriptive. Given the heterogeneity of the study questions and designs, a quantitative mathematical summary statistic was not calculated. Individual results were summarized where appropriate.

Results

Literature search

We identified 4059 articles, of which 1791 were duplicates. Of the remaining 2268 unique articles, 1305 were excluded based on their titles and abstracts (Fig. 1). Following full text review of the remaining 963 articles, a further 938 were excluded. The references of the remaining 25 articles were hand-searched for additional publications and one further relevant study was found. The results of the 26 studies are summarized in Table 1 found in the appendix.
| Year | Country      | Type of study     | Study population                          | Key findings                                                                                                                                                                                                 | Ref |
|------|--------------|-------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 2015 | USA          | Prospective survey| 25 intensive care units across 17 institutions | Caffeine intake minimisation was used in 32% of intensive care units as a pharmacological method to reduce delirium                                                                                          | 20  |
| 2017 | Iran         | Prospective RCT   | 80 patients; 40 coffee, 40 placebo         | 3.5 g coffee given via nasogastric tube in the mechanically ventilated patients increases the spontaneous respiratory rate and tidal volume but does not significantly affect other respiratory indicators.                  | 21  |
| 1987 | Germany      | Prospective observational | 12 male patients                      | Quinolones can inhibit the metabolism of caffeine and may cause higher levels of circulating caffeine and side effects                                                                                 | 22  |
| 1995 | Spain        | Prospective cohort| Liver impaired 33; normal liver 40        | Healthy individuals metabolise 3 mg IV caffeine faster than those with liver disease                                                                                                                       | 23  |
| 2017 | Greece       | Prospective cohort| 446 elective surgery patients             | In patients with no previous history of headache, caffeine consumption was an additional independent factor for postoperative headache                                                                   | 24  |
| 1994 | Denmark      | Prospective observational | 219 elective patients                     | The risk of post-operative headache was significantly greater in individuals with a daily caffeine intake > 400 mg/day                                                                                         | 25  |
| 2003 | United Kingdom| Prospective observational | 208 day patients                          | Caffeine is not a risk factor for peri-operative headache                                                                                                                                                | 26  |
| 1989 | New Zealand  | Prospective survey | 150 day case patients                     | Patient who consume > 200 mg caffeine/day were 3-fold more likely to have a headache post-operatively compared to those who did not                                                                         | 27  |
| Year | Country      | Type of study    | Study population | Key findings                                                                                                                                                                                                 | Ref |
|------|--------------|------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 1990 | Netherlands  | Prospective survey | 334 GA + 75 LA   | There was no difference between incidence of headache between GA or LA alone. Caffeine intake was not a risk factor for developing headache postoperatively.                                                                 | 28  |
| 1991 | New Zealand  | Prospective survey | 287 patients undergoing minor elective surgery | postoperative headache is related to caffeine intake and that this relationship is explained at least in part, by a perioperative caffeine withdrawal syndrome | 29  |
| 1993 | USA          | Prospective survey | 233 surgical outpatients | Among daily caffeine drinkers, those who drank caffeinated beverages on the day of the surgical procedure had a lower incidence of postoperative headaches than did those who abstained (17% versus 28%; P < 0.04) | 30  |
| 1994 | Switzerland  | Case report       | Elective open abdominal surgery for oophorectomy | 28F with post-operative headache, hemihypaesthesia, cerebral oedema on CT-Head which resolved with caffeine/ergometrine                                                                                      | 31  |
| 1995 | Switzerland  | Prospective RCT   | 40 patients; 20 caffeine, 20 placebo | Surgical patients who have high caffeine intake were randomised to taking oral caffeine tablets or placebo. No patients on caffeine supplements develop headaches while 10 (50%) on placebo developed headaches which lasted up to 7 days. | 32  |
| 1997 | USA          | Prospective RCT   | 234 elective surgical patients | prophylactic postoperative 200 mg IV caffeine decreased the incidence of headache                                                                                                                                 | 33  |

**Caffeine withdrawal and administration on induction and emergence from anaesthesia**

| Year | Country      | Type of study    | Study population | Key findings                                                                                                                                                                                                 | Ref |
|------|--------------|------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 2019 | United Kingdom | Prospective observational | 40 ASA 1 individuals | high daily caffeine intake is associated with lower propofol requirements for induction. We hypothesise that those with high daily caffeine intake have lower arousal levels before surgery, because of a relative caffeine deficit secondary to being nil-by-mouth | 38  |
| Year | Country | Type of study       | Study population                          | Key findings                                                                                                                                                                                                 | Ref |
|------|---------|---------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 1984 | USA     | Prospective RCT     | 60 patients undergoing CABG                | Patients who drank >3 cups of coffee/day, smoke >40 cigarettes/day and drank 1–3 ounces of alcohol required more fentanyl at induction for their CABG operation                                                      | 39  |
| 1984 | Australia | Prospective observational | 23 patients + 23 controls                  | High caffeine intake resulted in worse cognitive functioning post anaesthetic compared to low caffeine intake                                                                                                   | 45  |
| 2011 | USA     | Case report         | Elective tumour resection                  | The use of 500 mg IV caffeine intra-operatively to ensure the patient is responsive enough to perform intraoperative language mapping. Frequent stimulation-induced seizures thereafter limited further testing.                                    | 40  |
| 2017 | USA     | Case report         | Elective dental procedure                  | Use of 60 mg IV caffeine in an 16yo male with trisomy 10 with a history of slow emergence from anaesthesia to speed up emergence from anaesthesia and as a respiratory stimulant                                            | 41  |
| 2010 | Egypt   | Prospective RCT     | 60 patients                                | Administration of 500 mg IV caffeine decreases the number of patients who developed adverse post extubation respiratory events and hastens recovery from sevoflurane anaesthesia.                             | 44  |
| 2018 | USA     | Prospective RCT     | 8 males patients                           | 15 mg/kg IV caffeine is able to accelerate emergence from isoflurane anaesthesia in healthy males without any apparent adverse effects                                                                             | 42  |
| 2018 | USA     | Retrospective observational | 151 heavily sedated patients in the post-anaesthesia recovery area | Median of 150 mg IV caffeine may enhance the speed of recovery following general anaesthesia without any respiratory or cardiovascular changes                                                                       | 43  |

**Safety and changes associated with caffeine administration**

| Year | Country | Type of study       | Study population                          | Key findings                                                                                                                                                                                                 | Ref |
|------|---------|---------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 1996 | USA     | Prospective survey | 882 nurses surveyed                      | 85% of responders would withhold caffeine in patients after an acute myocardial infarction as a part of coronary precautions                                                                                             | 34  |
### Characteristics

The 26 articles retrieved were grouped into themes of caffeine in the ICU\textsuperscript{20–23} and caffeine in the perioperative setting\textsuperscript{24–45}. These were further subdivided into withdrawal headaches or delirium, effect on induction and emergence from sedation and safety/changes associated with caffeine administration. This included 3 case reports\textsuperscript{31,40,41}, 14 studies with 1-199 participants\textsuperscript{21–23,27,32,35–39,42–45}, seven studies with 200–500 participants\textsuperscript{24–26,28–30,33}, one with 500–1000 participants\textsuperscript{34} and one study that surveyed 25 intensive care units across 17 institutions\textsuperscript{20}.

#### Caffeine use in the intensive care unit

There were four studies investigating the use of caffeine in the intensive care unit, including a national survey and three studies which administered caffeine to ICU patients\textsuperscript{20–23}. Dzerba \textit{et al} performed a national survey of 25 ICUs across 17 institutions in the United States of America to evaluate the delirium screening tools and protocols in place to reduce the incidence of delirium. Afternoon caffeine minimisation was utilised in 32% of ICUs to reduce delirium and improve sleep\textsuperscript{20}.

One study investigated caffeine administration on induction or emergence from sedation in the ICU. Sadat \textit{et al} randomised 80 mechanically ventilated ICU patients to either receive 3.5 g of coffee in 100 mL of water or placebo (100 mL of distilled water) at 10 am in the morning\textsuperscript{21}. There was a significant increase in spontaneous respiratory rate and tidal volumes at 30 minutes and 60 minutes in patients who received coffee compared to placebo\textsuperscript{21}.

Two studies investigated other effects of caffeine. The first study found concomitant administration of quinolones and caffeine in 12 ICU patients could inhibit the metabolism of caffeine resulting in higher plasma levels\textsuperscript{22}. The second study was a randomised controlled trial that administered 3 mg/kg caffeine...
to assess liver function in 33 ICU patients with impaired liver function and 40 with normal liver function\textsuperscript{23}. Individuals with impaired liver function had significantly longer elimination of caffeine compared to those with normal liver function. Neither study reported on any adverse events of caffeine administration\textsuperscript{22,23}.

### Caffeine use in the peri-operative period

There were 22 studies investigating caffeine use in the peri-operative period\textsuperscript{24–44}. There were 10 studies investigating the effect of caffeine peri-operatively and the development of post-operative headache\textsuperscript{24–33}. Seven investigated caffeine withdrawal\textsuperscript{24–33} and three studies administered oral caffeine to prevent post-operative headache\textsuperscript{31–33}. Of the seven prospective studies investigating the effect of caffeine withdrawal, five studies found caffeine withdrawal increased the incidence of post-operative headache\textsuperscript{24–33}. Three studies investigated the administration of caffeine to relieve post-operative headache\textsuperscript{31–33}. There was one case report of the successful administration of caffeine and ergometrine to relieve a post-operative headache\textsuperscript{31}. There were two prospective randomised controlled trials which found prophylactic caffeine administration decreased the incidence of post-operative headache\textsuperscript{32,33}.

Eight studies investigated induction and emergence from anaesthesia\textsuperscript{38–44}. Individuals who had a high caffeine intake required less propofol for induction\textsuperscript{38,39}, but greater opioids for induction for cardiac surgery\textsuperscript{45} and lower cognitive scores post-operatively\textsuperscript{45}. Furthermore, five studies found the administration of intravenous (IV) caffeine enhanced emergence from anaesthesia\textsuperscript{40–44}. Two case reports used IV caffeine to enhance emergence from sedation. The first study in a 52-year old male who received 500 mg IV caffeine to facilitate intra-operative language mapping who was slow to emerge after anaesthesia was ceased\textsuperscript{40}. The second case study was a 16-year old male who underwent a dental procedure using sevoflurane anaesthesia who experienced ongoing hypopnea and desaturation up to 90 minutes after the procedure. Caffeine was used (60 mg or 0.8 mg/kg) and resulted in increased alertness, no further desaturation, increased respiratory rate and tidal volumes\textsuperscript{41}. Gouda et al randomised 60 patients undergoing uvulopalatopharyngoplasty for treatment for obstructive sleep apnoea to either receive 500 mg IV caffeine or saline\textsuperscript{44}. Individuals who received caffeine had significantly faster time to extubation and fewer post-extubation respiratory complications (supraglottic obstruction, laryngospasm, reintubation, breath holding, desaturation)\textsuperscript{44}. Similar results were demonstrated by Fong et al, who randomised eight patients to receive IV caffeine at 7.5 mg/kg or saline and demonstrated caffeine resulted in significantly faster emergence from isoflurane anaesthesia\textsuperscript{42}. This study reported no adverse outcomes from administration of caffeine\textsuperscript{42}. Warner et al performed a retrospective audit of caffeine administration (median dose of 150 mg) in the post-anaesthetic recovery area to increase alertness in 151 heavily sedated patients\textsuperscript{43}. There was a significant improvement in sedation scores with no change in respiratory or cardiac outcomes and no reported adverse events\textsuperscript{43}.

There were four studies that investigated the safety and changes associated with caffeine administration\textsuperscript{34–37}. Intra-operative or post-operative caffeine may increase the incidence of post-operative nausea/vomiting\textsuperscript{36,37}. Intra-operative caffeine was found not to affect the incidence of post-operative
atrial fibrillation 37 and reduce time to spontaneous voiding post indwelling bladder catheter removal post-operatively 35. A national survey of 882 nurses found that 85% still practised caffeine restriction in patients after an acute myocardial infarction 34.

Discussion

In this review we systematically identified only 26 studies that examine caffeine therapeutic use and/or withdrawal in the ICU and perioperative settings. Furthermore, only four studies investigating the use of caffeine in the intensive care unit. This is somewhat surprising considering that withdrawal from caffeine in other settings has been extensively described in the literature for almost 200 years 46, 47. Furthermore, given the commonality of use of caffeine products and its broad range of psychoactive and physiologic effects, it may be expected to have significant applications in critical care and perioperative medicine. Despite this, there is a paucity of clinical studies investigating withdrawal or administration of caffeine in the intensive care setting, and use of caffeine to facilitate emergence from anaesthesia or use in the peri-operative period.

Onset of caffeine withdrawal occurs as early as 12–24 hours post abstinence, with symptoms lasting between 2 to 9 days 18. It is unsurprising that when chronic caffeine users are admitted to hospital and are required to fast for surgery, they develop a caffeine withdrawal headache post-operatively. Administration of caffeine peri-operatively can reduce the incidence of post-operative headache due to caffeine withdrawal. In the intensive care setting, these patients are also likely withdrawing from caffeine. Currently, there are no studies investigating caffeine withdrawal in the intensive care setting. Although the typical effects of caffeine may not be seen, the effect on circadian rhythm, cognition and mood may be impaired which may contribute to delirium. Caffeine minimisation is one strategy used both in the community and the intensive care setting to reduce the incidence of delirium 20, 48. In the community, current strategies to reduce delirium include caffeine minimisation after midday. One pilot study across 21 nursing homes and one dementia special care unit found eliminating caffeine intake in the afternoon and evening resulted in significant improvement in sleep scores but no change in agitation/aggression, irritability and aberrant motor behaviour 48. However, administration of caffeine earlier in the day may help reset and normalise circadian rhythm 49, 50.

Caffeine can facilitate emergence from sedation or anaesthesia. In the intensive care setting, administration of caffeine has been shown to increase spontaneous breathing in intubated patients, which may help wean patients from mechanical ventilation 21. Post-operatively, caffeine has been used to facilitate emergence from anaesthesia 40–43. Administration of caffeine to reduce time to emergence from anaesthesia has been demonstrated in animal studies 42, 51, 52. Increasing emergence from anaesthesia to assist with respiratory drive and return of upper airway tone would be helpful in high risk patients, such as the morbidly obese, individuals with severe obstructive sleep apnoea, or those who are more susceptible to opioid medications with respiratory depression effects. A similar process may occur in adults emerging from anaesthesia that has been suggested in infants, in which caffeine acts centrally
on the medullary respiratory centre to increase sensitivity to carbon dioxide demonstrated in infants \(^9\) and may offset the effects from opioids and other sedative medications. The use of caffeine and its derivatives are not routinely used nor are they licensed for the use to facilitate emergence from anaesthesia in adults. Due to the small number of studies included, that used a wide range of caffeine dosing (60 mg to 500 mg), it is unclear what dose will be effective to facilitate emergence from anaesthesia. There is growing interest in the effects of caffeine habits on induction of anaesthesia and in the use of caffeine to increase recovery and emergence from anaesthesia. Individuals with high caffeine intake (> 3 cups/day) may require lower doses of induction agents (including opiates and sedative agents such as propofol), which is thought to be due to caffeine dependence and withdrawal resulting in lower arousal pre-operatively \(^{38,39}\). Additionally, individuals with high caffeine intake were shown to have worse cognitive functioning post-anaesthesia, likely from caffeine dependence \(^{45}\). The use of caffeine in the ICU setting has the benefit of reducing excessive daytime somnolence and removing barriers to participate in daytime physiotherapy.

The secondary beneficial effects of caffeine administration could be exploiting in the ICU setting. Gastrointestinal dysmotility is a common problem in the intensive care patients, compounded by opiates, surgery, sepsis and electrolyte abnormalities \(^{53}\). Caffeine has been shown to effectively improve gastrointestinal motility with no significant side effect \(^{54}\). Caffeine intake has been historically limited in peri-operatively in patients due to the risk of vasospasm and risk of cardiac events \(^{55,56}\). However, caffeine use after an acute myocardial infarct may be reduce the risk of cardiovascular mortality \(^{57,58}\) and does not increase risk of atrial fibrillation after cardiac surgery \(^{37}\). At rest, caffeine appears to promote generalised vasodilation and does not affect digital microvascular perfusion \(^{59,60}\), however it does result in reduced cerebral blood flow \(^{61,62}\). Future studies investigating the use of caffeine in the ICU setting should be aware of these secondary effects particular in patients who have undergone neurological or plastic reconstructive procedures or have had a recent stroke.

As a scoping review, the major limitation is the inability to perform systematic analysis between groups due to the heterogeneity of papers and themes found. Advantages of this review include no language limitation, inclusion of grey research (i.e. conference abstracts) and a thorough search using a comprehensive search strategy designed by a with the assistance of an expert medical librarian.

### Conclusion

In conclusion, we identified some areas of caffeine use but this is largely an under investigated area. Caffeine withdrawal due to hospitalisation occurs rapidly and patients can develop withdrawal symptoms including headache. Administration of caffeine or coffee supplementation has been shown to be safe, can result in faster emergence from anaesthesia. This scoping review has highlighted gaps in the literature regarding the use of caffeine in the intensive care unit and in the peri-operative period. Studies examining mitigation of withdrawal effects of caffeine use, optimal dosing, preferred route of
administration (ie parenteral versus oral) and therapeutic use of caffeine as adjunctive therapies for pain management and delirium are a priority.

**Abbreviations**

ICU: Intensive Care Unit

IV: Intravenous

**Declarations**

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Not applicable.

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