Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Sedation and Anesthesia Options for Diagnostic Procedures: A Review of Clinical Effectiveness and Guidelines

DATE: 08 May 2015

CONTEXT AND POLICY ISSUES

Diagnostic imaging procedures, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), are an integral piece to the delivery of effective health care to Canadians. They assist clinicians in identifying the presence and cause of disease, assessing the nature of the disease, designating the appropriate course of treatment and monitoring the effects of interventions. The number of diagnostic imaging tests conducted has been increasing rapidly given improvements in technological progress. In 2010, it was estimated that 4.3 million CT tests and 1.4 million MRI tests were conducted in Canada, representing nearly a doubling in numbers compared to 2004 estimates.[1]

When used appropriately, diagnostic tests permit more rapid and accurate determination of the causes of a patient's symptoms to ensure that the appropriate and clinically-relevant care is delivered. However, not all patients may be suitable for diagnostic imaging. In particular, it has been a challenge to conduct diagnostic procedures on patients who cannot stay still due to sleep apnea; movement disorders; claustrophobia; cognitive decline or impairment and in pediatric patients or those with special needs. Image acquisition often requires a patient to lie still for a long period and, in these patients, diagnosis may be complicated by movement artefacts and non-compliance. In extreme circumstances, additional diagnostic sequences may be necessary, scans may be aborted or patients may simply refuse to undergo imaging. Missed or increasingly difficult scans can have both clinical and financial implications.[2,3] Consequently, an option for these patients is sedation (defined by the Canadian Anesthesiologists' Society[4] as "a state of reduce excitement or anxiety") and anesthesia (defined as "a state of total unconsciousness").[4] The provision of therapeutic sedation or anesthesia may make unpleasant procedures more acceptable to patients although there may also be potential risks including life-threatening complications.

The purpose of this rapid review was to assess the available evidence regarding the clinical effectiveness of sedation and/or anesthesia options in patients undergoing diagnostic procedures who are required to be still. Furthermore, guidelines on sedation and anesthesia in patients undergoing diagnostic procedures were identified and assessed.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still?

2. What are the evidence-based guidelines associated with sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still?

KEY FINDINGS

The use of sedatives and anesthetics may be suitable for certain procedures although there is considerable heterogeneity in the studies identified. Propofol-based regimens may be effective in reducing both the recovery and procedure time compared to traditional sedatives in adults undergoing diagnostic endoscopy while the value of local anesthesia in adults undergoing CT/MR-arthrography remains unclear. Among pediatrics, the evidence suggests that sedation/anesthesiology can be safe and efficacious for a variety of diagnostic procedures. One clinical practice guideline, specific to pediatrics, stated that the pharmacological choice should take into account patients' needs and preferences although, chloral hydrate or midazolam were recommended for patients undergoing painless imaging given its wider safety margin.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including OVID Medline, PubMed, The Cochrane Library (2015, Issue 4), ECRI databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses randomized controlled trials, observational studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to documents published between January 1, 2010 and April 14, 2015.

Selection Criteria and Methods

One reviewer screened the search results to identify relevant publications, including: health technology assessments (HTAs); systematic reviews (SRs) and meta-analyses (MA); randomized controlled trials (RCTs); observational studies; and clinical practice guidelines (CPGs). The initial screen was based on title and abstract, which was followed by a full-text screen of any potentially relevant articles. Studies considered for inclusion were based on the selection criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adult and pediatric patients undergoing diagnostic procedures who are required to remain still
Intervention	Sedation and anesthesia options (e.g., equipment, gases, drugs, including standard of care)
Comparator	Drugs (drug regimens) Standard of care No comparator
Outcomes	Clinical effectiveness (e.g., additional sedation if patients wake up, clinical benefits and harms); guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, observational studies, clinical practice guidelines

Exclusion Criteria

Articles were excluded if there were a duplicate report of the same study; if they were already included in a selected SR or HTA; if they were published prior to 2010; or if they did not meet the specified inclusion criteria (Table 1). Non-English reports were excluded. Diagnostic technologies for image-guided surgery were also excluded.

Critical Appraisal of Individual Studies

SRs were appraised using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist.[5] Items considered in the AMSTAR checklist include: a priori design of the review; duplicate independent reviewers; a priori defined eligibility criteria; comprehensive search of information sources; transparent reporting of study selection; clear presentation of study characteristics; assessment of studies' quality; scientifically-sound interpretation of the results; appropriate methods to combine data from studies; assessment of publication bias; and reporting of funding sources.[5]

Randomized and non-randomized controlled trials were appraised using the Downs and Black checklist.[6] Concepts evaluated within this 27-item checklist included: reporting; external validity; internal validity and; power.[6]

Guidelines were appraised using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.[7] The items included in the AGREE instrument include: scope and purpose of the guideline; stakeholder involvement; rigor of development; clarity and presentation; applicability; and editorial independence.[7]

In conducting the critical appraisal, an overall numeric score was not calculated for each study. Rather, the selected instrument was used as a tool to identify strengths and weaknesses that were subsequently reviewed narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature review identified 158 citations in which 34 potentially relevant reports were selected for full-text review following the initial title and abstract screen. Grey literature search further retrieved two additional records resulting in a total of 19 publications that satisfied the pre-specified inclusion criteria (Table 1). These consisted of three SRs,[8-10] 13 RCTs,[7,11-22] two observational studies [23,24] and one CPG.[25] No HTA reports were identified that met the above-specified selection criteria. The PRISMA flowchart[26] detailing the study selection process is presented in Appendix 1. Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

A summary of the study characteristics table is provided in Appendix 3.

<u>Comparative clinical effectiveness and safety of sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still</u>

A total of 19 studies addressed either the comparative clinical or safety of sedation or anesthesia in patients undergoing diagnostic procedures. Among these publications, three were SRs,[8-10]13 were RCTs,[7,11-22] two were cohort studies,[23,24] and one was a CPG.[25] All SRs,[8-10] the majority of pediatric RCTs[7,11,13,14,18,19,21,22] and both observational studies[23,24] addressed safety and efficacy outcomes whereas, the adult RCTs focused solely on outcomes of clinical efficacy.[12,15,17]

Country of Origin

The three SRs were published by authors from Australia,[10] Canada,[9] or China[8] that identified individual trials conducted in numerous different jurisdictions. In terms of the RCTs, the three adults trials were conducted in Austria,[17] South Korea,[15] or USA.[12] Of the ten pediatric trials, two each were conducted in USA,[7,18] Iran [14,19] and India,[11,22] while one each was conducted in Denmark,[16] Saudi Arabia,[21] Slovenia,[13] and Turkey.[20] With respect to the three observational studies, two each were conducted in USA[23,27] and the remaining was conducted in Turkey.[24] The majority of trials were conducted in a single-center [7,12,13,15-19,21] with the exception of one study that involved two study sites.[11] The two cohort studies were two-arm trials: one each originating from USA [23] or Turkey.[24]

Patient Population

Adults:
Two of the SR were focused on adult patients: one on endoscopic retrograde cholangiopancreatography[8] and the other on all endoscopy procedures (i.e., colonoscopy, esophagogastroduodenoscopy, gastrointestinal endoscopy).[9] Both SRs searched a broad range of electronic databases and grey literature sources.[8,9] However, the one by Bo et al.[8] did not impose any language or search timeframe restrictions (i.e., database inception to October 2010) while the one by Kamel et al.[9] was restricted to English-only publications dating from the past five years (i.e., January 2005 to July 2010). In terms of study characteristics, the SR by Bo et al.[8] identified six relevant RCTs involving 663 subjects in which 331 received propofol while 332 received another sedative agent. These six studies involved less than 100 participants per

treatment arm (i.e., sample size ranging from 32 to 197). The SR by Kamel et al.[9] identified three SRs, 15 RCTs and three CPGs of relevance. The sample size in the individual trials ranged from 44 to 314 participants. Three RCTs focused on adults[12,15,17] The RCTs on adults all shared similar scope in that patients were recruited to study the clinical efficacy of local anesthesia for MR[12,15,17] or CT[15] shoulder arthrography.

Pediatrics:
One SR evaluated interventions to reduce pain and distress in a pediatric patients undergoing voiding cystourethrography.[10] Although both electronic databases and grey literature sources were searched without language restrictions, the search date range was not reported. Among the eight studies identified, five focused on pharmacological interventions. The sample size in the pharmacological studies ranged from 47 to 139 patients. Ten RCTs[7,11,13,14,16,18-22] and two observational cohort studies[23,24] studied pediatric populations. The trials primarily addressed the impact of sedation or anesthesia for children scheduled for CT[11,14,20,24] or MRI,[7,16,18-24] with the exception of two studies that either evaluated gastrointestinal endoscopies[13] or nuclear medicine techniques (i.e., diethylene triamine pentaacetic acid renal scintigraphy).[24] The purpose of sedation or anesthesia varied across studies. Some RCTs focused their assessment on different pre-anesthetic sedatives prior to introducing an intravenous (i.v.) cannula that would deliver a common anesthetic agent.[11,20,22] The purpose of others were to assess the impacts of sedation/anesthesia over the entire duration of the diagnostic procedure (i.e., both induction and maintenance) [7,13,21,23,24]. Additional studies evaluated the clinical effectiveness of single-dose agents to induce sedation[14,19] or the clinical effectiveness of continuous drug infusion to maintain anesthesia.[16,18]

Interventions and Comparators

Both SRs in the adult population focused on sedation: Bo et al.[8] compared propofol against traditional sedatives (i.e., meperidine, scopolamine, midazolam, pentazocine individually or as a combination therapy) while Kamel et al.[9] identified all studies on short-acting and dissociative sedative agents. The SR in the pediatric population by Rao et al.[10] broadly included any interventions, such as pharmacological, psychological or other, that would reduce pain and/or distress in patients undergoing voiding cystourethrography. All studies had a placebo-control arm that was compared with pharmacological agents, including midazolam, chloral hydrate and fentanyl.

The RCT on adults evaluated local anesthesia, such as lidocaine,[17] mepivacaine,[15] and ropivacaine.[12] In two of these studies, the comparator was saline[12,15] while the comparator was no anesthesia in the remaining study.[17] The RCTs that focused on a pediatric population were mostly two-arm studies that evaluated sedatives and/or general anesthesia for induction and/or maintenance therapy. With the exception of one study that had a placebo comparator,[20] the remaining RCTs involved an active control. The sedatives studied in the pediatric population include midazalom, [11,14,19-21] chloral hydrate[14,19,21] and dexmedetomidine.[7,22] Anesthetics studied include ketamine,[13,22] isoflurane,[18] sevoflurane,[16] and propofol (alone[7,18] or as combination agent with opioids such as remifentanil[16] or sedatives such as midazolam[11,13]).

Both cohort studies were active comparator trials in which four pharmacological agents were evaluated: dexmedetomidine versus. pentobarbital in one study[23] and midazolam versus propofol in the other.[24]

Evidence-based guidelines and recommendations on sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still

One CPG was identified that was issued in 2010 by the National Institute for Clinical Excellence (NICE) in the UK[25] and was reviewed in 2012. This guideline broadly addressed sedation options in children and young people (i.e., under the age of 19 years) undergoing both diagnostic and therapeutic procedures. The guideline's working group consisted of independent experts from a broad range of medical expertise (e.g., anesthetist, nurses, dental practitioner, gastroenterologist, radiologist, health psychologist) along with patient representation. The guideline addressed a broad spectrum of patient management and provided research recommendations in areas that lacked evidence, such as: assessment factors to determine a patient's need for sedation, the type of training required by clinicians delivering sedation and the clinical effectiveness of combination therapy. The recommendations were generated from a systematic literature review and appraised by GRADE. No CPGs were identified within the search timeframe that discussed sedation/anesthesia in adult undergoing diagnostic procedures.

Summary of Critical Appraisal

A summary of the results of the critical appraisal are presented in Appendix 4.

Comparative clinical effectiveness and safety of sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still

Systematic Reviews

The three SRs shared certain commonalities. For instance, a comprehensive set of databases and grey literature sources was searched. In two studies, the search strategy was not provided which limits the ability to assess whether the search was indeed appropriately designed.[8,10] The study selection was done in duplicate although one SR failed to mention whether this was done independently.[8] Characteristics of the included studies were either summarized by a table[8,10] or narratively.[9] A limitation common across the SRs was that a list of excluded studies was not provided as part of the report.

Another SR reported the use of an explicit tool to guide their critical appraisal. Bo et al.[8] used the Jadad scale and found that the majority of the selected studies were of good or high quality (i.e., four out of the six studies attained a Jadad score ≥3). Rao et al.'s critical appraisal was based on the Cochrane Risk of Bias tool in which one study had a low risk of bias.[10] Although the majority of pharmacological studies preserved allocation concealment, they often did not blind the primary outcome assessor and it remained unclear whether outcome reporting was complete. As Kamel et al.[9] did not use an explicit tool, their critical appraisal was less systematic. Appraisal was not consistent as some concepts were evaluated in certain studies but not discussed in others. Some of the concepts evaluated include blinding, sample size, outcome measure and external validity. While one SR did address publication bias,[8] this may be considered inappropriate as only five studies were identified as part of their review.[28] Two SRs did not disclose whether any potential conflict of interest were present.[8,10]

Randomized Controlled Trial

All 13 RCTs explicitly described the inclusion/exclusion criteria for their patient populations and the interventions studied with outcome assessment standardized across treatment groups. Although randomization was stated, in over half of the studies, it was difficult to evaluate whether it was conducted appropriately. Two studies reported imbalances in baseline prognostic factors between the treatment groups.[7,16] In nearly half of the studies, the baseline patient characteristics for each treatment groups were not adequately provided,[17,18,20,22] and the authors did not conduct any statistical tests to test similarity between groups.[11,13] Three studies explicitly stated that they maintained allocation concealment.[16,18,21] However, it is likely that some studies did ensure allocation concealment through their reports of online randomization[12,19,22] or by the use of opaque sealed envelopes [11] Blinding was mentioned in nearly all of the studies.[7,11-16,18-22] It was inconsistent which groups were blinded during the conduct of the trials: the patients[12,15,16,20-22]; the clinician.[12,20-22] and/or the outcome assessor (i.e., the data collectors or outcome adjudicators)[7,11,14,16,18-22] The risk of attrition bias in most trials was low given that the study duration typically did not go beyond the sedation/anesthesia period. The only exception was pediatric studies that excluded patients due to study protocol deviations,[11] incomplete documentation,[13,21] or protocol nonadherence.[7] A handful of the RCTs, all of which involved pediatric patients, calculated their sample size that would be required for adequate power[11,14,16,18,21,22] although, in one study,[11] they did not reach its a priori sample size.

Observational Studies

The quality of the conduct and reporting of the observational studies was of concern.[23,24] The sample size was not calculated to ensure that the studies were adequately powered. As both were positive studies, the concern about being underpowered is that such studies are more likely to have higher false positive rates (i.e., results incorrectly indicate statistical significance) and may leave a false impression of the true difference between treatment groups. It is hard to assess the impact of selection bias as convenience sampling was used and, at most, a small set of baseline patient characteristics were reported. Although both studies did not find any statistically significant difference in their demographic parameters, gender was close to the conventionally quoted margin of statistical significance (p=0.06) in one of the studies.[24] Meanwhile, in the other study, statistically significant differences exist between the treatment groups in terms of what body parts were imaged.[23] The statistical analyses were not adjusted for any differences in baseline characteristics nor corrected to account for multiple comparisons. The potential impact of confounders is high and was not addressed in either study. As blinding was not mentioned, it is uncertain if patients, clinicians and outcome assessor were not blinded, possibly leading to an increased risk of performance and detection biases. Although attrition was not an issue given the short study duration (i.e., time to procedure discharge), the observational study by Sebe et al.[24] was a retrospective cohort that excluded patients with missing data. As the study did not report on the potential reasons for the missing data nor the characteristics of the patients that were excluded, it is unclear whether patients with missing data were systematically different from those with no missing data who were included in the analysis. If the prognostic factors between these groups were different, this may reduce this study’s generalizability.

Evidence-based guidelines and recommendations on sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still

The NICE guideline[25] was based on a systematic literature review of reports published as early as 1950s. Since its first iteration, the evidence was updated to include literature published up to March 2012. Both clinical and economic issues were included in the search with a detailed search strategy provided in the appendices. However, screening was often conducted by one reviewer and checked by a second reviewer when necessary. Although the guideline development involved both disease experts and patient representatives, no declaration of their potential conflict of interests was provided. It appears that the strength of the evidence for each recommendation was assessed according to Grading of Recommendation Assessment, Development and Evaluated (GRADE) even though the actual result from GRADE was not provided. The draft guideline underwent both public consultation and an external guideline review panel with a broad membership, including clinical expert, industry and public representation. As alluded above, renewal of the guidelines were explicitly mentioned for every three years after publication, and the evidence was indeed updated in 2012.

Summary of Findings

Detailed summary of findings are presented in Appendix 5.

Comparative clinical effectiveness and safety of sedation and anesthesia options for adult undergoing diagnostic procedures who are required to remain still

Clinical outcomes: Sedative and anesthesia options in adults undergoing diagnostic procedures

Two SRs addressed sedation in patients undergoing endoscopy procedures and both reached similar conclusions. The meta-analysis by Bo et al.[8] found that propofol sedation was associated with statistically significantly reduced time to recovery (weighted mean difference: -18.69, 95% confidence interval (CI): -25.44 to -11.93) and a trend towards shorter procedure time (mean difference: -8.05, 95% CI: -16.74 to 0.63) in patients undergoing endoscopic retrograde cholangiopancreatography. This was supported by the narrative SR by Kamel et al.[9] The addition of adjuvants, such as meperidine and midazolam fentanyl, was found to further decrease recovery time.[9]

Three RCTs addressed local anesthesia in adult patients undergoing either MR or CT arthrography. Two of these studies found no difference in pain between the treatment (10 mg lidocaine or 1.5 mL of mepivacaine 2%) and control group,[15,17] whereas one study found that the addition of 10mL of ropivacaine 0.5% resulted in significantly lower pain reports.[12] The study on ropivacaine further report no differences in the number of patients requiring repeat sequences and the time required for MR imaging and time taken for the actual fluoroscopic procedure.[12]

Safety outcomes: Sedative and anesthesia options in adults undergoing diagnostic procedures

A meta-analysis found no significant difference in the rates of hypotension (odds ratio (OR): 1.69, 95% CI: 0.82 to 3.50) and hypoxia (OR: 0.90, 95% CI: 0.55 to 1.49) between propofol compared to traditional sedative agents.[8] The conclusions were aligned with the second SR as propofol did not increase the rates of hypoxia, respiratory depression, arrhythmias, hypotension and colonic perforations.[9]

No studies that addressed the safety of anesthesia in adult patients prior undergoing a diagnostic procedure were identified.

Comparative clinical effectiveness and safety of sedation and anesthesia options for children undergoing diagnostic procedures who are required to remain still

Given the heterogeneity in the pediatric population studies, the order in which results were reported are based on the potential quality of the evidence (i.e., systematic review, randomized controlled trials, observational studies) and grouped by the purpose of sedation and/or anesthesia (i.e. induction and/or maintenance).

Clinical outcomes: Sedative and anesthesia options in children undergoing diagnostic procedures

Most RCTs identified in the SR by Rao et al.[10] found that midazolam reduced distress in children undergoing voiding cystourethrography with no impact on the technical aspects of the procedure. One study found that patients receiving nitrous oxide (n=23) compared with patients receiving midazolam (n=24) had more rapid onset of sedation and shorter recovery time (34 min, $P < 0.001$). One placebo-controlled RCT was identified by Rao et al.[10] in which fentanyl was found to be no different to placebo in reducing pain for children undergoing voiding cystourethrography.

Three RCTs[7,13,21,23,24] and both cohort studies[23,24] investigated options to induce and maintain sedation/anesthesia in children over the entire duration of their diagnostic procedure. Different pharmacological agents were studied by each study. The RCT included: midazolam + ketamine versus ketamine,[13] dexmedetomidine versus propofol,[7] and chloral hydrate versusmidazolam[21] while the observational studies studied: propofol versus midazolam[24] and dexmedetomidine versus pentobarbital.[23] The trial by Brecelj et al.[13] found no difference in clinical efficacy (i.e., need for supplemental anesthesia or physician-rated appropriateness of sedation) between midazolam + ketamine compared with ketamine monotherapy in patients undergoing gastrointestinal endoscopies. Wu et al.[7] found that dexmedetomidine required statistically longer time than propofol to induce anesthesia, recover and overall the total procedure time. MRI scan time was longer in patients receiving dexmedetomidine than propofol by 10 minutes although this result was not significant. Propofol was associated with statistically fewer MRI disruptions due to body movements, technique failure; a lower pediatric anesthesia emergence delirium (PAED) total score; and statistically higher parental satisfaction. The PAED is a scale that assesses five items (i.e., eye contact, purposeful actions, awareness of the surroundings, restlessness and inconsolability) with a higher score corresponding to an higher degree of emergence delirium.[16] Hijazi et al.[21] noted that chloral hydrate was associated with a statistically significant shorter time to achieve sedation and recovery time compared to midazolam despite the longer duration of sedation. Furthermore, choral hydrate was found to offer a higher success rate and less likely to require a second dose to achieve sedation. The observational cohort study by Teshome et al.[23] found that both dexmedetomidine and pentobarbital could be used successful for procedural sedation although the recovery and sedation time was shorter for dexmedetomidine. The other cohort study provided consistent findings. Not only did propofol achieved sedation quicker and was associated with a shorter time to sedation and stay in the emergency room, patients on propofol had a significantly higher score on the Ramsay sedation scale.[24] The Ramsay sedation scale is a six-point scale that measures patient's responsiveness with a higher score indicative of a deeper level of sedation. No patients in the propofol group required additional drug beyond what was indicated in the study protocol while 10% of patients on midazolam required additional sedation ($P = 0.01$).[24]

In terms of the efficacy of single-dose sedation, two RCTs by the same group of authors addressed this by comparing midazolam versus chloral hydrate prior to a CT scan[14] and chloral hydrate + hydroxyzine versus chloral hydrate + midazolam prior to an MRI.[19] Chloral hydrate was found to be more effective than midazolam in inducing sedation: 93% of children achieved a Ramsay sedation score of four compared to 40% of patients on midazolam ($P < 0.001$). Similarly, more patients successfully completed the CT scan when administered chloral hydrate than midazolam.[21] No differences were observed between treatment groups in terms of the total and procedure time. Combination therapy of chloral hydrate with either hydroxyzine or midazolam was not difference with respect to clinical efficacy except that children on chloral hydrate + hydroxyzine stayed on average 22.8 minutes longer in the radiology department than those receiving chloral hydrate + midazolam ($P < 0.03$).[19]

Three RCTs evaluated the efficacy of sedatives as pre-medication prior to insertion of an i.v. cannula for general anesthesia in children scheduled for either an MRI/CT procedure. Gyanesh et al.[22] found that the MRI procedure time was overall similar between children randomized to ketamine, dexmedetomidine and saline. In terms of the acceptance of needle placement, anesthesiologist's and parental satisfaction, total propofol dose and quality of MRI favored the active treatment groups compared to the saline group. There were no differences between the two active-treatment groups across the outcomes studied. Demir et al.[20] randomized patients scheduled for outpatient CT/MRI to either midazolam (referred to as the "multiphase" sedation group) or placebo prior to attempting i.v. access. All reported outcomes (i.e., recovery time, parental anxiety, parental satisfaction, number of i.v. attempts, preparation room stay and need for additional propofol) favoured multiphase sedation. Lastly, Jain et al.[11] conducted a three arm study comparing midazolam, midazolam + ketamine and placebo in patients undergoing CT. The number of patients crying during venipuncture, sedation score, venipuncture score and parental satisfaction all favored the active treatment groups than the placebo control. More children in the placebo arm moved during the scan and more movement artifacts were noted although no patients required a subsequent scan. These results were statistically significant. The number of venipuncture attempts, mean dose of ketamine for maintenance of sedation and time to discharge were comparable across all three groups.

In contrast, two trials assessed continuous drug infusion options to maintain anesthesia in children undergoing MRI.[16,18] Patients receiving propofol had a longer time to eye opening and time to full wakefulness compared with isoflurane although the times to induction of anesthesia, complete MRI scan and discharge were similar between groups.[18] No patients in either group required a repeat sequence due to movement as image quality were reported as either good to excellent. Pedersen et al.[16] compared propofol-remifentanil with sevoflurane. Patients randomized to the propofol-based anesthesia had a shorter time to discharge. However, 15 patients receiving propofol-remifentail moved during the scan, while no movement were observed in the sevoflurane group ($P < 0.001$). Most patients that moved required further induction by thiopental. Sixteen percent in the propofol group and 24% in the sevoflurane group required an increase in the infusion rate or drug concentration given their vital parameters indicated insufficient anesthesia. The pediatric anesthesia emergence delirium scale was significantly lower in patients receiving propofol than sevoflurane ($P < 0.01$), with a lower score being more favorable. No differences were observed in parent-reported satisfaction.

Safety outcomes: Sedative and anesthesia options in children undergoing diagnostic procedures

In studies investigating pharmacological options for induction and maintenance of sedation and anesthesia, no severe adverse events were observed.[7,13,21,23,24] In one RCT, the majority of adverse events were short-term and balanced between the treatment groups with the exception of emergence reactions that occurred more frequently in patients receiving dual therapy with midazolam + ketamine compared to ketamine monotherapy ($P = 0.02$).[13] Another RCT reported higher rates of paradoxical agitation in patients receiving midazolam while mean arterial blood pressure greater than 25% from baseline was more common in patients receiving chloral hydrate.[21] In both an RCT and a cohort study, the reported adverse events related to dexmedetomidine were oxygen desaturation.[7,23] The cohort study found that dexmedetomidine had a lower incidence of adverse event (0.9%) than pentobarbital (4.5%) ($P = 0.08$). The most common adverse events associated with pentobarbital was emergence delirium and oxygen desaturation.[23] No complications were reported in patients receiving propofol in these studies [7,24]

With respect to single-dose sedation, more patients on chloral hydrate experienced a mild adverse effect (10%) than patients on midazolam (3.3%) although the results were not statistically significant.[14] If chloral hydrate was administered as a combination therapy, more adverse events were observed in patients receiving chloral hydrate + hydroxyzine (1/30, 3.3%) than in patients receiving chloral hydrate + midazolam (3/30, 10%)($P <0.04$).[19] None of the adverse events observed were classified as serious.

Two three-armed RCTs addressed the safety of sedation prior to performing i.v. cannulation to introduce a common anesthetic. Both studies[11,22] reported no difference in the frequency of adverse events between groups (ketamine versus dexmedetomidine versus saline[22] and midazolam versus midazolam+ketamine versus placebo[11]).

One study reported on the safety of anesthesia as maintenance therapy. Patients on propofol had significantly fewer all-cause adverse events (risk difference: 37%, 95% CI: 23 to 50%) than patients on isoflurane with adverse events occurring during the emergence and recovery period for both agents.[18]

Evidence-based guidelines and recommendations on sedation and anesthesia options for patients undergoing diagnostic procedures who are required to remain still

The NICE guideline[25] covers a variety of topics including: drug recommendations, pre-sedation assessment (e.g., communication, patient information, consent), fasting, patient’s psychological preparation, personnel and training, discharge criteria and clinical environment/monitoring. The guidelines noted that no sedatives had been approved in the pediatric population in the UK. Physicians, therefore, were advised to use the drug summary and the British National Formulary, alongside consideration of a patient’s needs and preferences, to determine the most appropriate sedative. Suitability for sedation is based on several factors, such as medical condition, weight (and growth assessment), past medical problems, current and previous medications and any previous allergies and physical, psychological and developmental status. For patients, who were unable to tolerate painless imaging, chloral hydrate (for children under 15 kg) and midazolam are first recommended given their wider margin of safety followed by propofol and sevoflurane given their narrower margin of safety. Ketamine and opioids are not routinely used. For patients undergoing gastrointestinal endoscopy, i.v. midazolam can be used to achieve minimal or moderate sedation or fentanyl (or equivalent opiod) with i.v. midazolam can be used to achieve moderate sedation. Specialist advice should be obtained before delivering sedatives in patients where concerns exist about potential airway or breathing problems or have an American Society of Anesthesiologists (ASA) grade ≥ 3 or for infants/neonates.

Limitations

In terms of the clinical and safety evidence, several studies were identified although, considerable heterogeneity was found in terms of its scope, patient population, imaging modalities and interventions studied. It is uncertain whether the study findings can be generalized at an aggregate level to a general "class" effects or whether the clinical effectiveness observed is agent specific. Similarly, it is hard to conclude whether the clinical effectiveness for sedation/anesthesiology can be generalized across to other diagnostic procedures or are limited to the specific diagnostic test in which patients underwent. Further work is required, including meta-analysis with appropriate subgroup analysis where suitable, to address some of the aforementioned questions.

So far, existing studies have been powered to detect differences in efficacy but not on safety outcomes. As such, it is difficult to ascertain whether the safety profile is indeed different between pharmacological agents. Given the smaller sample sizes, it is further unlikely that rarer events would have been uncovered. Additional studies, such as well-designed registries or observational studies, may be able to collect a sufficient number of patients such that differences between groups and rare events are detected.

The results of the critical appraisal of the RCTs suggested reporting issues associated with their methods and/or study findings For instance, nearly half did not sufficiently report on the baseline characteristics of each treatment group and many required deciphering on whether allocation concealment was preserved. Similar issues were found in terms of the statistical analysis and whether intention-to-treat or per protocol analysis was followed. Fewer observational studies were identified in this review although both suffered from methodological concerns that led to a higher risk of biases, such as selection bias, performance bias, detection bias, and confounding.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

This rapid response addressed the evidence surrounding the clinical effectiveness and practice guidelines on sedation or anesthesia options in patients undergoing diagnostic procedures. Eighteen comparative studies were identified across a wide spectrum of diagnostic procedures including: endoscopy, MRI, CT, X-ray (i.e., voiding cystourethrography) and nuclear medicine technique (i.e, renal scintigraphy). The existing evidence suggests that propofol reduces both recovery and procedure time compared with traditional sedatives in adults undergoing diagnostic endoscopy without differences in adverse event rates between the groups. The addition of adjuvants to a propofol-based regimen may reduce recovery time and provide greater satisfaction. Only ketamine, as monotherapy or combined with midazolam, has been studied in pediatric patients undergoing gastrointestinal endoscopy. Although ketamine monotherapy was safe and efficacious, combination therapy with midazolam was found to reduce the need for supplemental sedation and fewer emergence reactions.

With respect to MRI-based and CT-based procedures, the evidence on pain reduction is inconsistent as two studies reported no differences between adults receiving local anesthesia (i.e., lidocaine, mepivacaine) compared with those without anesthesia (e.g., placebo); while one study found improvements in pain reports in patients that received ropivicaine. In the pediatric population, studies found that the administration of a sedative had no differential impact on time-related parameters regardless of MRI or CT procedure but did provide improvements in terms of patient satisfaction, patient's acceptance of needles, the quality of diagnostic scan and lower doses of maintenance anesthesia. Generally, few statistical significant differences were observed between sedative/anesthetic agents with respect to safety in patients undergoing MRI or CT. Some evidence exists suggesting that propofol administered as induction and/or maintenance, was associated with shorter time to anesthesia induction, recovery and procedure completion and fewer reports of adverse events. In contrast, midazolam was generally associated with a longer time to achieve sedation and recover period compared to other agents. A systematic review found that midazolam effectively alleviated procedure-related distress in pediatric patients undergoing X-ray although fentanyl was no better than placebo in shortening the recovery time.

The evidence-based guideline, specific to pediatrics, recommended that chloral hydrate or midazolam should be considered as first-line agents given their wider safety margin, followed by propofol or sevoflurane given their narrower margin. The administration of ketamine and opioids was not recommended when undergoing painless imaging.

In conclusion, the evidence suggests that the use of sedatives and anesthetics may be suitable for certain procedures although there remains considerable heterogeneity in the included studies in terms of its scope, patient population, imaging modality and intervention studied. For these reasons, the results must be interpreted with great caution.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES:

1. Canadian Institute for Health Information. Medical imaging in Canada 2012 [Internet]. Ottawa: The Institute; 13 A.D. Feb 12. [cited 2015 Apr 29]. Available from: http://www.cihi.ca/CIHI-ext-portal/pdf/internet/MIT_SUMMARY_2012_en

2. Dewey M, Schink T, Dewey CF. Claustrophobia during magnetic resonance imaging: cohort study in over 55,000 patients. J Magn Reson Imaging. 2007 Nov;26(5):1322-7.

3. Melendez JC, McCrank E. Anxiety-related reactions associated with magnetic resonance imaging examinations. JAMA. 1993 Aug 11;270(6):745-7.

4. Position paper on procedural sedation: an official position paper of the Canadian Anesthesiologists' Society [Internet]. Toronto: Canadian Anesthesiologists' Society; 2015. Appendix 6. [cited 2015 May 7]. Available from: http://www.cas.ca/English/Page/Files/97_Appendix%206.pdf

5. Serafini G, Ingelmo PM, Astuto M, Baroncini S, Borrometi F, Bortone L, et al. Preoperative evaluation in infants and children: recommendations of the Italian Society of Pediatric and Neonatal Anesthesia and Intensive Care (SARNePI). Minerva Anestesiol. 2014 Apr;80(4):461-9.

6. Goodwin JA, Kudo K, Shinohe Y, Higuchi S, Uwano I, Yamashita F, et al. Susceptibility-Weighted Phase Imaging and Oxygen Extraction Fraction Measurement during Sedation and Sedation Recovery using 7T MRI. J Neuroimaging. 2014 Dec 16.

7. Wu J, Mahmoud M, Schmitt M, Hossain M, Kurth D. Comparison of propofol and dexmedetomedine techniques in children undergoing magnetic resonance imaging. Paediatr Anaesth. 2014 Aug;24(8):813-8.

8. Bo LL, Bai Y, Bian JJ, Wen PS, Li JB, Deng XM. Propofol vs traditional sedative agents for endoscopic retrograde cholangiopancreatography: a meta-analysis. World J Gastroenterol. 2011;17(30):3538-43.

9. Kamel C, Moulton K, Cunningham J. Short-acting agents and dissociative agents for conscious sedation during endoscopy procedures: systematic review of clinical and cost-effectiveness and guidelines [Internet]. Ottawa: CADTH; 2010. [cited 2015 Apr 17]. Available from: https://www.cadth.ca/sites/default/files/pdf/M0020_Sedation_for_Endoscopy_L3_e.pdf

10. Rao J, Kennedy SE, Cohen S, Rosenberg AR. A systematic review of interventions for reducing pain and distress in children undergoing voiding cystourethrography. Acta Paediatr. 2012 Mar;101(3):224-9.

11. Jain K, Ghai B, Saxena AK, Saini D, Khandelwal N. Efficacy of two oral premedicants: midazolam or a low-dose combination of midazolam-ketamine for reducing stress during intravenous cannulation in children undergoing CT imaging. Paediatr Anaesth. 2010 Apr;20(4):330-7.

12. Fox MG, Petrey WB, Alford B, Huynh BH, Patrie JT, Anderson MW. Shoulder MR arthrography: intraarticular anesthetic reduces periprocedural pain and major motion artifacts but does not decrease imaging time. Radiology. 2012 Feb;262(2):576-83.

13. Brecelj J, Trop TK, Orel R. Ketamine with and without midazolam for gastrointestinal endoscopies in children. J Pediatr Gastroenterol Nutr. 2012 Jun;54(6):748-52.

14. Fallah R, Nakhaei MH, Behdad S, Moghaddam RN, Shamszadeh A. Oral chloral hydrate vs. intranasal midazolam for sedation during computerized tomography. Indian Pediatr. 2013 Feb;50(2):233-5.

15. Choo HJ, Lee SJ, Kim DW, Choi SJ, Lee IS. Intraarticular local anesthesia: can it reduce pain related to MR or CT arthrography of the shoulder? AJR Am J Roentgenol. 2013 Apr;200(4):860-7.

16. Pedersen NA, Jensen AG, Kilmose L, Olsen KS. Propofol-remifentanil or sevoflurane for children undergoing magnetic resonance imaging? A randomised study. Acta Anaesthesiol Scand. 2013 Sep;57(8):988-95.

17. Spick C, Szolar DH, Reittner P, Preidler KW, Tillich M. MR arthrography of the shoulder: do we need local anesthesia? Eur J Radiol. 2014 Jun;83(6):980-3.

18. Heard C, Harutunians M, Houck J, Joshi P, Johnson K, Lerman J. Propofol anesthesia for children undergoing magnetic resonance imaging: a comparison with isoflurane, nitrous oxide, and a laryngeal mask airway. Anesth Analg. 2015 Jan;120(1):157-64.

19. Fallah R, Fadavi N, Behdad S, Fallah TM. Efficacy of chloral hydrate-hydroxyzine and chloral hydrate-midazolam in pediatric magnetic resonance imaging sedation. Iran. 2014;j. child. neurol.. 8(2):11-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058059

20. Demir G, Cukurova Z, Eren G, Tekdos Y, Hergunsel O. The effect of "multiphase sedation" in the course of computed tomography and magnetic resonance imaging on children, parents and anesthesiologists. Rev Bras Anestesiol. 2012 Jul;62(4):511-9.

21. Hijazi OM, Ahmed AE, Anazi JA, Al-Hashemi HE, Al-Jeraisy MI. Chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children. Saudi Med J. 2014 Feb;35(2):123-31.

22. Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial. J Anesth. 2014 Feb;28(1):12-8.

23. Teshome G, Belani K, Braun JL, Constantine DR, Gattu RK, Lichenstein R. Comparison of dexmedetomidine with pentobarbital for pediatric MRI sedation. Hosp. 2014 Nov;pediatr.. 4(6):360-5.

24. Sebe A, Yilmaz HL, Koseoglu Z, Ay MO, Gulen M. Comparison of midazolam and propofol for sedation in pediatric diagnostic imaging studies. Postgrad Med. 2014 May;126(3):225-30.

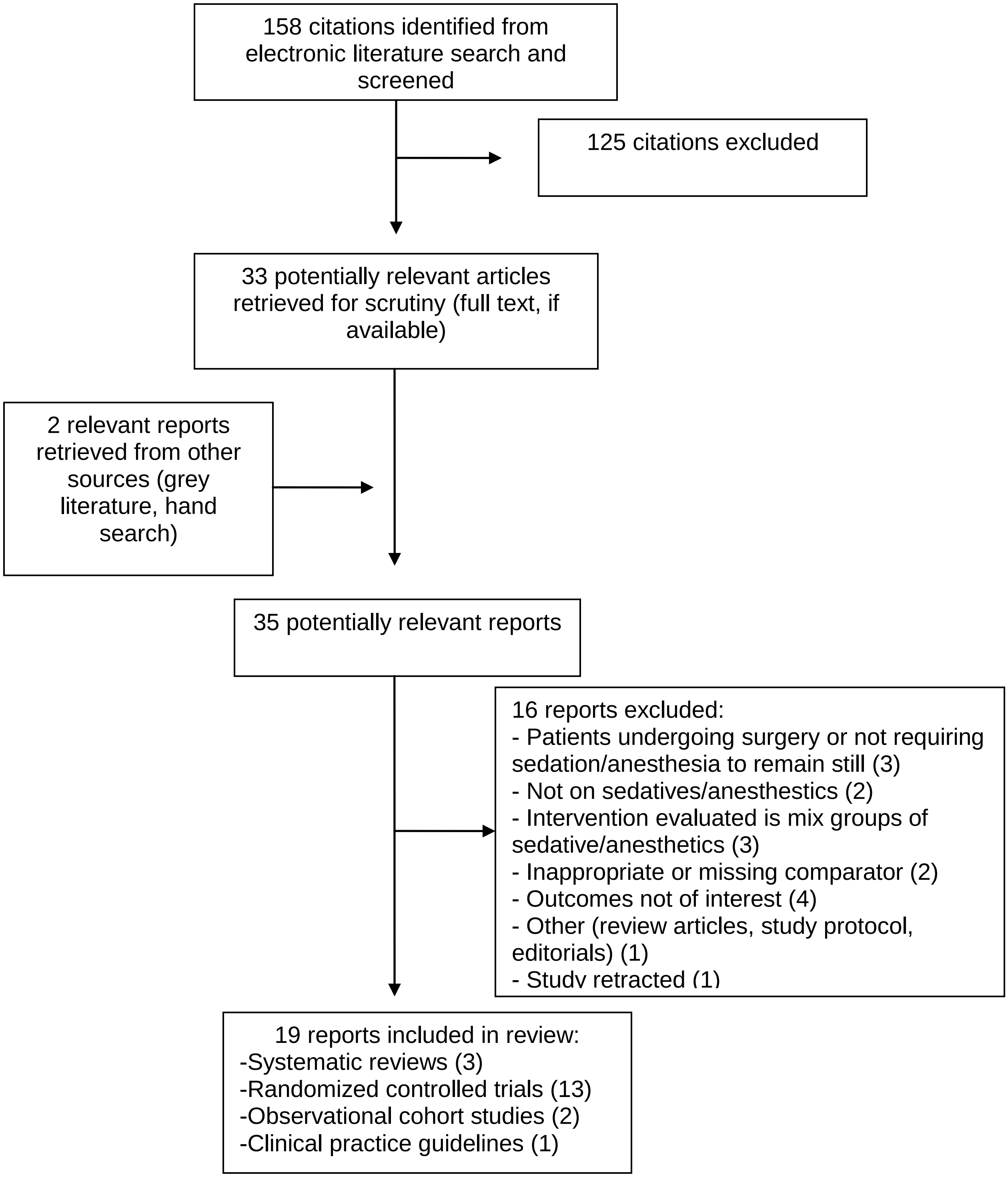
25. National Clinical Guideline Centre (UK). Sedation in Children and Young People: Sedation for Diagnostic and Therapeutic Procedures in Children and Young People. London: Royal College of Physicians (UK); 2010 Dec. (National Institute for Health and Clinical Excellence: Guidance).

26. Tornqvist E, Mansson A, Hallstrom I. Children having magnetic resonance imaging: A preparatory storybook and audio/visual media are preferable to anesthesia or deep sedation. J Child Health Care. 2014 Jan 31.

27. Tith S, Lalwani K, Fu R. Complications of three deep sedation methods for magnetic resonance imaging. J Anaesthesiol Clin Pharmacol. 2012 Apr;28(2):178-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3339721

28. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. [Oxford, United Kingdom]: The Cochrane Collaboration; 2011 Mar. [cited 2015 May 4]. Available from: http://www.cochrane-handbook.org

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional References of Potential Interest

Upcoming Trials

Pediatrics

Mekitarian FE, Robinson F, de Carvalho WB, Gilio AE, Mason KP. Intranasal Dexmedetomidine for Sedation for Pediatric Computed Tomography Imaging. J Pediatr. 2015 Mar 5. PubMed: PM25748567

Biomarkers or Technical Outcomes

Adults

Goodwin JA, Kudo K, Shinohe Y, Higuchi S, Uwano I, Yamashita F, et al. Susceptibility-Weighted Phase Imaging and Oxygen Extraction Fraction Measurement during Sedation and Sedation Recovery using 7T MRI. J Neuroimaging. 2014 Dec 16. PubMed: PM25511937

Pediatrics

Harreld JH, Helton KJ, Kaddoum RN, Reddick WE, Li Y, Glass JO, et al. The effects of propofol on cerebral perfusion MRI in children. Neuroradiology. 2013 Aug;55(8):1049-56. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3720819

DiFrancesco MW, Robertson SA, Karunanayaka P, Holland SK. BOLD fMRI in infants under sedation: Comparing the impact of pentobarbital and propofol on auditory and language activation. J Magn Reson Imaging. 2013 Nov;38(5):1184-95. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3695003

Wagner KJ, Schulz CM, Sprenger T, Pieper T, Heuser F, Hohmann CP, et al. Comparing propofol versus sevoflurane anesthesia for epileptogenic focus detection during positron emission tomography in pediatric patients. Minerva Anestesiol. 2013 Nov;79(11):1264-8. Available from: http://www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2013N11A1264

Clinical Practice Guidelines – Methodology Uncertain/ Not Provided

General

Merchant R, Chartrand D, Dain S, Dobson G, Murrek MM, Lagacé A, et al. Guidelines to the practice of anesthesia. Can J Anesth. 2014 Jan;61:46-71. Available from: http://www.cas.ca/English/Guidelines

Pediatrics

Slade S. Sedation (Pediatric): Diagnostic and Therapeutic Procedures. The Joanna Briggs Institute. 2014 Mar 16.

APPENDIX 3: Characteristics of Included Publications

First Author, Publication Year, Country	Study design	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
Systematic Reviews: Adults					
Bo, 2011,[8] China	SR of RCTs on comparative safety and efficacy of propofol for ERCP Included literature up to October 2010. No language restrictions	6 active-control trials: 663 adult patients	Propofol	Traditional sedative agents, such as: meperidine, scopolamine, midazolam, pentazocine (and its combination)	- Time: procedure and recovery - Complications (i.e. hypoxia and hypertension)
Kamel, 2010,[9] Canada	SR of SR/MA, RCTs, economic evaluation and CPGs on sedatives during endoscopy Search date: January 2005 to July 2010. Restricted to English	22 studies: Patient characteristics not provided. Consists of 3 SR/MAs, 15 RCTs, one economic evaluation and 3 CPGs	Any short-acting agents and dissociative sedatives, as single agents or in combination	Any short-acting agents and dissociative sedatives, as single agents or in combination	- Clinical effectiveness (e.g., patient or provider satisfaction, recovery or procedure time, patient safety) - Economic value
Systematic Reviews: Pediatrics					
Rao, 2012,[10] Australia	SR of RCTs on comparative safety and efficacy of interventions that reduce distress, pain or anxiety during voiding cystourethrography Search dates uncertain. No language restrictions	8 active-control trials: 591 pediatric patients, 67.7% female, mean age: 4.7 yrs	Pharmacological, psychological or other treatment aimed to reduce distress, pain or anxiety	Pharmacological, psychological or other treatment aimed to reduce distress, pain or anxiety	- Time: procedure - Distress - Pain or anxiety, reported by patient, parents, clinicians, technicians - Urological outcomes - Radiation exposure - Costs - Complications
Randomized Controlled Trials: Adults					
Spick, 2014,[17] Austria	Unblinded, single-center, expertise-based RCT	Total: 249 patients, 28.5% female, mean age: 44.4 ± 14.6 yrs	Lidocaine (1mL)	No anesthesia	- Pain (i.e., VAS)

First Author, Publication Year, Country	Study design	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
		Local anesthesia (n=61) Control 'Group B' - no anesthesia (n=92) Control 'Group C' – no anesthesia (n=96) Inclusion criteria: Patient undergoing shoulder MR arthrography			
Choo, 2012,[15] South Korea	Single-center RCT	Mepivacaine (n=60): 50% female, mean age: 48.7 yrs Saline (n=60): 40% female, mean age: 50.3 Inclusion criteria: Patients (≥16 yrs of age) undergoing shoulder MR or CT arthrography	Mepivacaine 2% (1.5 mL)	Saline	- Pain (i.e., VAS or VRS)
Fox, 2011,[12] USA	Outcome-assessor blinded, single-center RCT	Ropivacaine (n=70): 41.4% female Saline (n=70): 34.3% female Inclusion criteria: Patients (≥18 yrs of age) undergoing shoulder MR arthrography	Ropivacaine 0.5% (10mL)	Saline	- Pain (i.e., VRS) - Time: procedure - Repeat sequences - Quality of scan (i.e., degree of motion)
Randomized Controlled Trials: Pediatrics					
Heard, 2015,[18] USA	Outcome-assessor blinded, single-center RCT	Propofol/oxygen (n=75), 53.3% female, mean age: 4.5 yrs Isoflurane/nitrous oxide(n=70), 42.7% female, mean age: 4.4 yrs Inclusion criteria: ASA physical status I or II; fasting and unpremedicated; scheduled for elective MRI	*Induction*: Sevoflurane 8% /nitrous oxide70% *Maintenance:* Propofol/ oxygen (induction: 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$; maintenance: 250 $\mu g \cdot kg^{-1} \cdot min^{-1}$), nasal cannula	*Induction:* Sevoflurane 8% /nitrous oxide 70% *Maintenance:* Isoflurane 1.5%nitrous oxide 70%, laryngeal mask airway	- Time: procedure, cognitive impairment, recovery - Repeat sequences - Complications

First Author, Publication Year, Country	Study design	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
Fallah, 2014,[19] Iran	Outcome-assessor blinded, single-center RCT	Chloral hydrate + hydroxyzine (n=30), 43.3% female, mean age: 2.9 yrs Chloral hydrate + midazolam (n=30), 50% female, mean age: 2.5 yrs Inclusion criteria: Aged 1-7 yrs; ASA class I or II; scheduled for elective MRI	*Induction only:* Chloral hydrate (40 mg/kg) + hydroxyzine (2 mg/kg)	*Induction only:* Chloral hydrate (40 mg/kg) + midazolam (0.5 mg/kg)	- Time: sedation, procedure - Ramsay sedation scale - Proportion completed - Quality of MRI - Complications
Gyanesh, 2014,[22] India	Double blinded RCT	Dexmedetomidine (n=52), 32.7% female, mean age: 5.1 yrs Ketamine (n=52), 32.7% female, mean age: 4.9 yrs Saline (n=46), 45.7%female, mean age: 5.0 yrs Inclusion criteria: Aged 1-10 yrs; scheduled for MRI	*Induction:* •Dexmedetomidine (1 µg·kg^{-1}), intranasal *Maintenance:* • Midazolam (0.03 mg·kg^{-1}) + Glycopyrrolate (4 µg·kg^{-1}) + Propofol (1 mg·kg^{-1}), IV	*Induction:* • Ketamine (5 mg·kg^{-1}) , intranasal • Saline, intranasal *Maintenance:* • Midazolam (0.03 mg·kg^{-1}) + Glycopyrrolate (4 µg·kg^{-1}) + Propofol (1 mg·kg^{-1}), IV	- Time: procedure, recovery - Anesthesiologist and parent satisfaction - Quality of scan - Ease of cannulation - Complications
Wu, 2014,[7] USA	Single-center RCT	Propofol (n=49), 3.9 yrs Dexmedetomidine (n=46), mean age: 4.3 yrs Inclusion criteria: Aged 1-7 yrs; ASA class I or II; scheduled for outpatient MRI ≥75 min	*Induction:* • Propofol (2 mg ·kg^{-1}), IV *Maintenance:* • Propofol (200 µg·kg^{-1}·min^{-1}), IV	*Induction:* •Dexmedetomidine (2 µg·kg^{-1}), IV *Maintenance:* •Dexmedetomidine (2 µg·kg^{-1}·h^{-1}), IV	- Time: procedure, recovery - MRI stoppage and technique failure - PAED scale - Parental satisfaction - Complications
Hijazi, 2014,[21] Saudia Arabia	Double-blinded, single-center RCT	Chloral hydrate (n=144), 44.4% female, mean age: 2.2 yrs Midazolam (n=142), 38.7% female, mean age: 2.2 yrs Inclusion criteria: Aged ≤ 12 yrs;	*Induction:* • Chloral hydrate (75 mg·kg^{-1}), oral *Maintenance:* • Chloral hydrate (30 mg·kg^{-1}), oral	*Induction:* • Midazolam (0.5 mg·kg^{-1}), oral *Maintenance:* • Midazolam (0.25 mg·kg^{-1}), oral	- Time: sedation, recovery - Ramsay sedation scale - Successful sedation - Additional sedation - Complications

First Author, Publication Year, Country	Study design	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
		Required sedation for diagnostic procedure			
Pedersen, 2013,[16] Denmark	Single-blinded, single-center RCT	Propofol + reminfentanil (n=60), 43.3% female, mean age: 4.5 yrs Sevoflurane (n=60), 46.7% female, mean age: 4.6 yrs Inclusion criteria: Aged 1-10 yrs; ASA class I or II; scheduled for MRI	*Induction:* • Either Thiopental (5 to 10 mg·kg^{-1}), IV or Sevoflurane (8%)/ 100% oxygen, laryngeal mask airway *Maintenance:* • Propofol (56 µg·kg^{-1}·min^{-1}) + Remifentanil (0.06 µg·kg^{-1}·min^{-1}), IV	*Induction:* • Either Thiopental (5 to 10 mg·kg^{-1}), IV or Sevoflurane (8%)/ 100% oxygen, laryngeal mask airway *Maintenance:* • Sevoflurane (8%)/ 100% oxygen, laryngeal mask airway	- Number of patients staying longer than 60 min - Quality of scan (i.e., number of movements) - PAED scale - Parental satisfaction
Demir, 2012,[20] Turkey	Double-blinded RCT	Total: 100 patients, 42% female, mean age: 4.21 ± 2.9 yrs Midazolam (n=50) Placebo (n=50) Inclusion criteria: Aged 2-12 yrs; ASA class I or II; scheduled for outpatient CT/MRI	*Induction:* • Midazolam (0.5 mg·kg^{-1}), oral *Maintenance:* • Propofol, 1% (2 mg·kg^{-1}·min^{-1}), IV	*Induction:* • Placebo *Maintenance:* • Propofol, 1% (2 mg·kg^{-1}·min^{-1}), IV	- Time: recovery - Child's pain: Oucher scale - Parent state-Trait Anxiety Inventory - Parental satisfaction - Number of IV attemps - Additional anesthesia
Fallah, 2012,[14] Iran	Outcome assessor-blinded RCT	Midazolam (n=30), 43% female, mean age: 2.8 yrs Chloral hydrate (n=30), 36.7% female, mean age: 2.7 yrs Inclusion criteria: Aged 1-10 yrs; ASA class I or II; scheduled for outpatient elective CT	*Induction only:* • Midazolam (0.2 mg·kg^{-1}), intranasal	*Induction only:* • Chloral hydrate (100 mg·kg^{-1}), oral	- Time: procedure, recovery - Ramsay sedation scale - Parental satisfaction - Complications
Brecelj, 2011,[13] Slovenia	Single-blinded, single center RCT	Ketamine+Midazolam (n=97), 41.2% female, median age: 8.9 yrs Ketamine (n=104), 48.1% female, median age: 8.8 yrs Inclusion criteria: Aged 1-19 yrs; admitted for diagnostic endoscopy	*Induction:* • Ketamine (0.75 mg·kg^{-1}) + Midazolam (0.1 mg·kg^{-1}), IV *Maintenance:* • Ketamine (0.5 mg·kg^{-1}) every 10 to 15 min + Midazolam (0.05 mg·kg^{-1}) every 30 to 60 min, IV	*Induction:* • Ketamine (0.1 mg·kg^{-1}), IV *Maintenance:* • Ketamine (0.5 mg·kg^{-1}) every 10 to 15 min, IV	- Ketamine dosage - Complications

First Author, Publication Year, Country	Study design	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
Jain, 2010,[11] India	Double-blinded, two-center RCT	Midazolam-ketamine (n=31), 25.8% female, mean age: 3.3 years Midazolam (n=29), 34.4% female, mean age: 3.2 yrs Placebo (n=32), 40.6% female, 3.4 yrs Inclusion criteria: Aged 1-5 years; ASA class I or II; scheduled for CT	*Induction:* • Midazolam (0.25 $mg{\cdot}kg^{-1}$) + Ketamine (1 $mg{\cdot}kg^{-1}$), oral *Maintenance:* • Ketamine (1 to 1.5 $mg{\cdot}kg^{-1}$), IV	*Induction:* • Midazolam (0.5 $mg{\cdot}kg^{-1}$), oral • Placebo *Maintenance:* • Ketamine (1 to 1.5 $mg{\cdot}kg^{-1}$), IV	- Number of attempts at venipuncture - Sedation scores - Quality of scan - Repeat sequences - Parental satisfaction - Complications
Observational Studies: Pediatrics					
Teshome, 2014,[23] USA	Single-center cohort	Pentobarbital (n=154), 36% female, mean age: 3.5 yrs Dexmedetomidine (n=112), 38% female, mean age: 3.0 yrs Inclusion criteria: children who underwent MRI between May 2008 and October 2010	*Induction* • Pentobarbital (2 $mg{\cdot}kg^{-1}$), IV *Maintenance* • Pentobarbital (1 to 2 $mg{\cdot}kg^{-1}$ every three minutes; up to maximum of 7 $mg{\cdot}kg^{-1}$, IV	*Induction* • Dexmedetomidine (1 mg), IV *Maintenance* • Dexmedetomidine (1 mg), IV, if necessary	- Time: induction recovery, total - Failed sedation - Complications
Sebe 2013,[24] Turkey	Single-center cohort	Propofol (n=100), 42% female, mean age: 3.6 ± 2.6 yrs Midazolam (n=100), 33% female, mean age: 3.5 ± 3.2 yrs Inclusion criteria: Pediatric patient (age<14 years); ASA 1 and 2; scheduled for diagnostic procedure in radiodiagnostic and nuclear medicine	*Induction* • Propofol (2 $mg{\cdot}kg^{-1}$ for 2 mins), IV *Maintenance* • Propofol (100 $\mu g{\cdot}kg^{-1}{\cdot}min$), IV	*Induction* • Midazolam (0.15 $mg{\cdot}kg^{-1}$ for 2 to 3 mins), i.v. *Maintenance* • Midazolam (0.08 $mg{\cdot}kg^{-1}$ every 5 min if necessary), IV	- Time: induction, sedation, procedure, legth of stay in emergency department - Ramsay sedation scale - Complications

First Author, Publication Year, Country	Study design	Patients Characteristics, Sample Size (n)	Intervention (dosage strength)	Comparator(s)	Outcomes
Clinical Practice Guidelines					
NICE. Sedation in children and young people. 2010,[25] UK	CPG	Guideline developed from a literature search. Recommendations appraised using GRADE.	Medical therapies covered include: ketamine, opioids, chloral hydrate, midazolam, propofol, sevoflurane		Patient management (e.g., assessment, fasting, monitoring, discharge) Research recommendations

µg = microgram; ASA = American Society of Anesthesiology; CPG = clinical practice guidelines; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; FDG-PET = fluorodeoxyglucose positron emission tomography; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; IV = intravenous; kg = kilogram; MA= meta-analysis; MR = magnetic resonance; mg = milligram; min= minutes; MRI = magnetic resonance imaging; NICE = National Institute for Health and Care Excellence; PAED = Pediatric anesthesia emergence delirium scale; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; USA = United States of America; VAS = visual analog scale; VRS = verbal rating scale; yrs = years

APPENDIX 4: Critical Appraisal of Included Publications

First Author, Publication Year, Country	Strengths	Limitations
SRs: Adults		
Bo, 2011,[8] China	Explicit description of database included in the literature search and grey literature sources. Duplicate study selection performed although unclear whether this was done independently. Provides list of included studies alongside its characteristics. Critical appraisal of the included studies conducted according to the Jadad scale. Addressed heterogeneity in the conduct of the MA.	Search strategy was not provided. List of excluded studies not provided Publication bias considered by Funnel plot although this is inappropriate given that only five studies were identified. No disclosure of potential conflict of interest.
Kamel, 2010,[9] Canada	Explicit description of the database and grey literature sources. Search strategy was provided in an Appendix. Duplicate independent study selection performed. Characteristics of included studies summarized narratively. Provides a statement on funding sources although any author-specific potential conflict of interest is not provided	List of excluded studies not provided. No explicit mention of use of a critical appraisal tool to assess included studies. No assessment of potential publication bias.
SRs: Pediatrics		
Rao, 2012, [10] Australia	Explicit description of database included in the literature search and grey literature sources. Duplicate independent study selection performed. Provides list of included studies alongside its characteristics. Critical appraisal of the included studies conducted according to Risk of Bias scale	Search strategy described but exact strategy was not provided. List of excluded studies not provided Publication bias not considered although may not have been appropriate given study design. No disclosure of potential conflict of interest.

First Author, Publication Year, Country	Strengths	Limitations
RCTs: Adults		
Spick, 2014,[17] Austria	Explicit description of inclusion/exclusion criteria and the interventions studied. Randomization to clinical expert assignment. This expertise-based RCT minimizes differential expertise bias. Outcome assessment is valid and standardized across treatment. Some measures were taken to reduce bias (i.e., assessment of pain without the presence of the clinician). Statistical tests appear appropriate given that only a single outcome was assessed. Given the short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	Allocation concealment unclear. Blinding not mentioned and unlikely ensured. No calculation of sample size to ensure study had adequate power. Lack transparent reporting of patients' baseline characteristics, thereby unable to assess whether randomization was adequately conducted. This also limits external validity of study.
Choo, 2012,[15] South Korea	Explicit description of inclusion/exclusion criteria and the interventions studied. Block randomization conducted on a consecutive sample of patients. No observable differences were found in baseline characteristics. Outcome assessment is valid and standardized across treatment. Patients blinded on their assignment to prevent performance bias which was suitable given the objective nature of the outcomes. Transparent reporting of patients' baseline characteristics. Given the short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	Allocation concealment unclear. No calculation of sample size to ensure study had adequate power. Multiple independent comparisons were conducted without correction
Fox, 2011,[12] USA	Explicit description of inclusion/exclusion criteria and the interventions studied.	No calculation of sample size to ensure study had adequate power.

First Author, Publication Year, Country	Strengths	Limitations
	Online randomization which may have preserved allocation concealment. No observable differences were found in baseline characteristics. Outcome assessment is valid and standardized across treatment. Both patients and clinicians were blinded. This reduces the potential for performance and detection bias. Statistical tests adjusted by age, gender and baseline pain levels to account for underlying differences. Given the short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	Multiple independent comparisons were conducted without correction Lack transparent reporting of patients' baseline characteristics, thereby limits external validity of study.
RCTs: Pediatrics		
Heard, 2015,[18] USA	Explicit description of inclusion/exclusion criteria and the interventions studied. Randomization by random number table was prepared by an independent person not involved in the study. Allocation concealment explicitly noted to be preserved. Outcome assessment was standardized across treatment group. Outcome assessors were blinded to minimize detection bias. Conducted a priori sample size calculation in which adequate sample size was achieved. Statistical tests were Bonferroni-adjusted to account for multiple comparisons. Given the short study duration, no dropouts/loss-to-follow-up seemed to	Reported a few of the patients' baseline characteristics, Uncertain whether statistically significant differences exist in these prognostic factors. Blinding of patient and clinician not ensured. Although only one clinician performed every procedure, there is a risk of performance bias.

First Author, Publication Year, Country	Strengths	Limitations
	have occurred; in which case, study would be based on ITT principles.	
Fallah, 2014,[19] Iran	Explicit description of inclusion/exclusion criteria and the interventions studied. Online randomization, prepared by an independent person not involved in the study. This may have preserved allocation concealment. No observable differences found in baseline characteristics between groups. Outcome assessment was standardized across treatment group. Outcome assessors were blinded to minimize detection bias. No loss-to-follow-up occurred; study analysis based on ITT principles.	No calculation of sample size to ensure study had adequate power. Multiple independent comparisons were conducted without correction. Blinding of patient and nurse not ensured, resulting in a risk of performance bias. Lack transparent reporting of patients' baseline characteristics, thereby limits external validity of study.
Gyanesh, 2014,[22] India	Explicit description of inclusion/exclusion criteria and the interventions studied. Computer-generated randomization, which may have preserved allocation concealment. Outcome assessment was standardized. Patient, clinician and outcome assessor were blinded. This reduces the potential for performance and detection bias. Conducted a priori sample size calculation in which adequate sample size was achieved. Statistical tests were Bonferroni-adjusted to account for multiple comparisons. Given the short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	Lack transparent reporting of patients' baseline characteristics, thereby unable to assess whether randomization was adequately conducted. This also limits external validity of study.

First Author, Publication Year, Country	Strengths	Limitations
Wu, 2014,[7] USA	Explicit description of inclusion/exclusion criteria and the interventions studied. Outcome assessment was standardized across treatment group. Outcome assessors were blinded to minimize detection bias.	Method of randomization unclear. Even though few patients' baseline characteristics are reported, some prognostic factors were found to be statistically significant different. Lack of reporting may also limit study's external validity. Allocation concealment unclear. Blinding of patient and clinician not ensured, resulting in a risk of performance bias. No calculation of sample size to ensure study had adequate power. Multiple independent comparisons were conducted without correction Per protocol analysis conducted as excluded patients with protocol nonadherence.
Hijazi, 2014,[21] Saudia Arabia	Explicit description of inclusion/exclusion criteria and the interventions studied. Computer-generated random number randomization, prepared by an independent person not involved in the study. No observable differences found in baseline characteristics between groups. Allocation concealment explicitly noted to be preserved. Outcome assessment was standardized across treatment group. Patient, clinician and outcome assessor were blinded. This reduces the potential for performance and detection bias. Conducted a priori sample size calculation in which adequate sample size was achieved.	Multiple independent comparisons were conducted without correction Per protocol analysis conducted as excluded patients with incomplete data.
Pedersen, 2013,[16] Denmark	Explicit description of inclusion/exclusion criteria and the interventions studied.	Computer generated randomization. However, some prognostic factors were found to be statistically

First Author, Publication Year, Country	Strengths	Limitations
	Allocation concealment preserved. Outcome assessment was standardized across treatment group. Both patient and outcome assessors were blinded to minimize performance and detection bias. Conducted a priori sample size calculation in which adequate sample size was achieved. Statistical tests were Bonferroni-adjusted to account for multiple comparisons. Given the short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	significant different. Blinding of clinician not ensured. Lack transparent reporting of patients' baseline characteristics, thereby limits external validity of study.
Demir, 2012,[20] Turkey	Explicit description of inclusion/exclusion criteria and the interventions studied. Outcome assessment was standardized across treatment group. Patient, clinician and outcome assessors were blinded to minimize performance and detection bias. Given study short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	Allocation concealment unclear. Randomization performed although unclear whether it was done appropriately as baseline characteristics were not reported. No calculation of sample size to ensure study had adequate power. Multiple independent comparisons were conducted without correction Lack transparent reporting of patients' baseline characteristics, thereby limits external validity of study.
Fallah, 2012,[14] Iran	Explicit description of inclusion/exclusion criteria and the interventions studied. Computer-generated random number randomization, prepared by an independent person not involved in the study. No observable differences found in baseline characteristics between groups. Outcome assessment was standardized across treatment group.	Allocation concealment unclear. Blinding of patient and clinician not ensured, increasing risk of performance bias. Multiple independent comparisons were conducted without correction

First Author, Publication Year, Country	Strengths	Limitations
	Outcome assessors were blinded to minimize detection bias. Conducted a priori sample size calculation in which adequate sample size was achieved. Given the short study duration, no dropouts/loss-to-follow-up seemed to have occurred; in which case, study would be based on ITT principles.	
Brecelj, 2011,[13] Slovenia	Explicit description of inclusion/exclusion criteria and the interventions studied. Outcome assessment was standardized across treatment group.	Method of randomization unclear. Even though patients' baseline characteristics were reported, no statistical test performed to ensure treatment groups were similar. Allocation concealment unclear. Blinding mentioned as single blinded but uncertain who was blinded. No calculation of sample size to ensure study had adequate power. Multiple independent comparisons were conducted without correction Per protocol analysis conducted as excluded patients with incomplete documentation and receiving only colonoscopy. Uncertainty in the sample size for the outcome assessment one month post-sedation
Jain, 2010,[11] India	Explicit description of inclusion/exclusion criteria and the interventions studied. Allocation concealment maintained through use of opaque sealed envelopes. Outcome assessment was standardized across treatment group. Double-blinded but only explicitly report that outcome assessors were blinded. Uncertain who else was blinded.	Computer-generated random number chart employed to randomize patients. Even though patients' baseline characteristics were reported, no statistical tests were performed to ensure treatment groups were similar. A priori sample size calculation conducted. However, study failed to recruit the numbers required. Multiple independent comparisons were conducted without correction Statistical analysis based on per-

First Author, Publication Year, Country	Strengths	Limitations
		protocol analysis as patients were excluded following randomization for a variety of reason (numbers not balanced between study groups),
Observational Studies: Pediatrics		
Teshome, 2014,[23] USA	Explicit description of interventions studied, and standardization of outcome assessment. No drop out from this study. Statistical analysis as a result based on ITT principles. Variability in the point estimates reported as both standard deviation and ranges.	No mention on whether study subjects, clinicians and outcome assessors were blinded. Study not randomized. Furthermore, demographics and baseline characteristics between the two treatment groups were barely reported. Difficult to assess whether selection bias could have impacted the results and some factors were close to reaching statistical significance. No sample size calculation. Convenience sampling, which is highly vulnerable to selection bias. Statistical tests not adjusted to account for differences in baseline characteristics Did not correct statistically for multiple comparisons. Potential impact of confounders on study results not acknowledged.
Sebe 2013,[24] Turkey	Explicit description of characteristics of subjects, the interventions studied, and standardization of outcome assessment. Variability in some of the point estimates reported as standard deviation or through box-and-whiskers plot.	No mention on whether study subjects, clinicians and outcome assessors were blinded. Study not randomized. However, measured demographics and baseline characteristics between the two groups appear balanced. No sample size calculation. Included all patients in their records that had complete data and that satisfied the inclusion criteria. Convenience sampling, which is highly vulnerable to selection bias. As only included patients with

First Author, Publication Year, Country	Strengths	Limitations
		complete data, statistical analysis based on principles of per-protocol analysis. Statistical tests not adjusted to account for differences in baseline characteristics Did not correct statistically for multiple comparisons. Potential impact of confounders (e.g., imaging of different body parts) on study results not acknowledged.
Clinical Practice Guidelines: Pediatrics		
NICE. Sedation in children and young people. 2010,[25] UK	Clear description of scope and purpose. Intended target user for guideline clearly defined. Guideline development group includes individuals from relevant professional groups and patient representation. Methodology behind the literature review was explicitly reported including a copy of the search strategy. Single screening was conducted in most cases. Balanced consideration of efficacy and safety. Cost implications considered with publication of a costing report accompanying the study. Underwent public consultation in addition to external reviewers. Scheduled plan for updating guideline.	Appears to have used GRADE to assess the strength of the evidence as part of each recommendation although the results of this exercises are not provided. Conflicts of interests were not addressed.

CPG = clinical practice guidelines; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; ITT = intention-to-treat; MA = meta-analysis; NICE = National Institute for Health and Care Excellence; *P* = probability value; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; USA = United States of America

APPENDIX 5: Summary of Main Study Findings and Author's Conclusions

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
Systematic Reviews: Adults		
Bo, 2011,[8] China	• 6 RCTs comprising 663 patients (331 PRO vs. 332 traditional sedatives) • *Clinical efficacy:* ○ *Procedure time:* 3 studies, pooled MD: -8.05 min (95% CI: -16.74 to 0.63; *P* =0.07) ○ *Recovery time:* 5 studies, WMD: -18.69 min (95% CI: -25.44 to -11.93; *P*< 0.01) • *Safety:* ○ *Hypotension:* 4 studies, OR: 1.69 (95% CI: 0.82 to 3.50; *P* = 0.16) ○ *Hypoxia:* 4 studies, OR: 0.90 (95% CI: 0.55 to 1.49; *P* = 0.69)	"PRO sedation during ERCP leads to shorter recovery time without an increase of cardiopulmonary side effects. PRO sedation can provide adequate sedation during ERCP." (p. 2)
Kamel, 2010,[9] Canada	• 3 SR/MAs, 15 RCTs, one economic evaluation and 3 CPGs • *Clinical efficacy:* ○ In one SR/MA: PRO, compared to traditional sedatives, reduced recovery time (MD: -14.2 min, 95% CI: -17.6 to -10.8) and discharge time (MD: -0.76 min, 95% CI: -1.00 to -0.56); increased patient satisfaction (OR for dissatisfaction: 0.19, 95% CI: 0.16 to 0.55) without increasing adverse events (i.e., hypoxia, respiratory depression, arrhythmias, hypotension and colonic perforations) or impacting procedure time. ○ In one SR: Compared to MDZ-based therapy, PRO or PRO+adjuvants (e.g., meperidine, midazolam or fentanyl) associated with shorter recovery time (MD: 39.3 and 40.6 min respectively) and provide greater patient satisfaction • *Safety:* ○ Hypoxia: propofol vs. traditional sedatives, OR: 0.4 (95% CI: 0.2 to 1.49; *P* = 0.79) • *Clinical practice guidelines:* ○ Must ensure continuous patient monitoring during procedure and recovery period. ○ Adequately trained nurses and non-anesthesiological may safely administer sedatives during colonoscopy.	"PRO-based sedation may be more effective than sedation with traditional sedative agents and results in faster recovery times and shorter in-clinic time when used for conscious sedation during endoscopy… The evidence suggests that PRO for conscious sedation during endoscopy can be safely administered by non-anesthesiologists if there is proper training and adequate patient monitoring" (p.1)
Systematic reviews: Pediatrics		
Rao, 2012,[10] Australia	• 8 RCTs comprising 591 patients; 5 RCTs assessed pharmacological interventions comprising of 403 patients (208 pharmacological vs. 195 placebo) • *Clinical efficacy:* ○ Three out of the five studies found that MDZ reduced distress ○ One study found that patients receiving nitrous oxide (n=23) compared to MDZ (n=24) had more rapid sedation onset and shorter recovery time (34 min, *P* < 0.001) ○ Overall, the studies suggest that MDZ does not influence the technical aspects of voiding cystourethrography ○ No difference in pain scores between fentanyl and placebo	"Conscious sedation with MDZ effectively alleviates the distress of voiding cystourethrography in children older than 1 year of age…nitrous oxide 50% may be an alternative to MDZ, but further evidence is needed" (p.224)

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
RCTs: Adults		
Spick, 2014,[17] Austria	• 249 patients (Local anesthesia: 61 [Group A]; No anesthesia: 92 [Group B], 96 [Group C]) • *Clinical efficacy:* ○ *Pain intensity (VAS)*: No between group difference (Group A: 2.6; Group B: 2.6; Group C: 2.7)	"Local anesthesia is not required to lower a patient's pain intensity when applying intra-articular contrast media for MR arthrography of the shoulder. This could result in reduced costs and a reduced risk of adverse reactions, without an impact on patient comfort." (p.980)
Choo, 2012,[15] South Korea	• 120 patients (60 per group) • *Clinical efficacy:* ○ *Mean pain course*: No between group difference as both shower quadratic trend with peak at 2 hours after injection and baseline return at 2 days after injection ○ *Net pain score:* No difference at each phase (i.e., immediately, 2 hours, 1 day and 2 days after injection) ○ Subgroup analysis found no patient- or procedure-related condition— age, sex, history of shoulder arthroscopic surgery, baseline pain score, rotator cuff or labral tear, leakage of contrast agent, volume of injected contrast agent, level of difficulty of arthrography, physician experience, and imaging modality —affecting the efficacy of anesthesia	"intraarticular injection with 1.5 mL of 2% mepivacaine … did not reduce arthrography-related pain" (p. 866)
Fox, 2011,[12] USA	• 140 patients (70 per group) • *Clinical efficacy:* ○ *MR imaging time*: No difference between group (Local anesthesia: 27.5±5.5 min; saline: 28.6±5.5 min) ○ *Fluoroscopic procedure*: No difference between group (Local anesthesia: 18.9±15.4s; saline: 23.2±25.1s) ○ *Adjusted pre- and post-MRI imaging pain levels*: Local anesthesia had significantly lower levels of pain (MD: -0.8, 95% CI: -1.5 to -0.1) although, if exclude patients imaged by faster protocol, statistical difference disappears (MD: -0.8, 95% CI: -1.5 to 0) ○ *Repeat sequences*: No difference between groups (Local anesthesia: 23 patients; saline: 29 patients) ○ *Adjusted number of patients with motion in scan*: Half of the radiologists noted statistically significant difference in number of patients with ≥1 MR sequence rated as having moderate/severe motion	"The addition of ropivacaine 0.5% to the arthrography solution significantly decreases patient pain and major patient motion but does not reduce total MR imaging time or the number of patients requiring repeat sequences." (p. 583)
Randomized Controlled Trials: Pediatrics		
Heard, 2015,[18] USA	• 150 patients (75 per group) • *Clinical efficacy:* ○ *Induction, procedure and recovery time:* No between	"Adverse events… after PRO anesthesia with nasal cannula were less

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	treatment-group difference ○ *Early recovery time:* Longer for PRO than after isoflurane (time to eye opening: 20 (PRO) vs 14 mins (isoflurane), *P* < 0.01). ○ *Repeat sequence:* No repeat sequence due to movement in either groups was required. Image quality reported as good to excellent. • *Safety:* ○ *Frequency of all AE*: PRO significantly less than isoflurane (RD: 37%, 95% CI: 23 to 50%) ○ *Frequency of nausea/vomiting*: PRO significantly less than isoflurane (RD: 14%, 95% CI: 5.7 to 25.2%) ○ *Hemodynamics:* No statistical difference between treatment groups. ○ No AE during maintenance of anesthesia and AE only detected during emergence and recovery. ○ Airway events occurring between scan completion and transport to postanesthesia care unit occurred less frequently after PRO than isoflurane. ○ Oropharngeal airway not required in children anesthetized with PRO but required in 5 children anesthetized with isoflurane.	frequent than after isoflurane/N2O/LMA, although hemodynamic responses and recovery characteristics were similar. These data favor the use of a PRO infusion with supplemental oxygen by nasal cannula for healthy children without active upper respiratory tract infection undergoing anesthesia for MRI scans and other nonpainful procedures approximately 1 hour in duration" (p. 163)
Fallah, 2014,[19] Iran	• 60 patients (30 per group) • *Clinical efficacy:* ○ *Induction and procedure time:* No between treatment-group difference (*P* = 0.2 to 0.1) ○ *Time in radiology department:* Longer time for parents of children receiving CH-MDZ (69.1 min) than parents of children receiving CH-hydroxyzine (91.9 min) (*P* = 0.03) ○ *Adequate deep sedation and completion of MRI:* No treatment-group difference (CH-MDZ: 76.7%; CH-hydroxyzine: 73.7%; *P* = 0.76). ○ *Quality of MRI*: Not statistically different between treatment groups • *Safety:* ○ *Frequency of all AE*: More frequent in CH-MDZ group (*P* = 0.04) ○ No serious AEs observed in either groups	"Combinations of CH-hydroxyzine and CH-MDZ were effective in pediatric MRI sedation; however, CH-hydroxyzine was safer." (p 11)
Gyanesh, 2014,[22] India	• 156 patients (52 KET vs. 52 DEX vs. 46 saline) • *Clinical efficacy:* ○ *Procedure time*: Similar across all groups ○ *Acceptance of needle placement:* Most children in KET and DEX group exhibited minor or no withdrawal symptoms (*P* < 0.01 compared to saline). No between group differences between KET and DEX. ○ *Anesthesiologist and parental satisfaction*: Significantly higher in active-treatment arms than saline (*P* < 0.01) although no difference between active treatments ○ *Requirement of PRO:* Significantly higher dose required in saline group than both active-treatment groups (*P* < 0.02) ○ *Quality of MRI*: Significantly higher in KET and DEX group than saline group (*P* < 0.05). No difference between KET and DEX groups (*P* = 0.13) • *Safety:* ○ *Hemodynamics:* Remained similar at presentation,	"Intranasal administration is pain free and more acceptable to children and their parents. Both DEX and KET e are effective by this route. DEX, however, has to be given at least an hour before the procedure, which may pose problems in the busy schedule of the MRI suites. KET is as effective as DEX for this purpose." (p. 17)

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	throughout the procedure and 3 hours after MRI completion ○ *Frequency of AE:* Similar b groups (*P* = 0.137).	
Wu, 2014,[7] USA	• 99 patients with four subsequently removed due to protocol nonadherence (49 PRO vs. 46 DEX) • *Clinical efficacy:* ○ *Time*: DEX significantly longer than PRO with respect to anesthesia induction, emergence time, recovery time and total time (*P* <0.01). MRI scan time was 10 minutes longer with DEX (91.5 min) than PRO (81.7) (*P* = 0.08) ○ *Incidence of MRI interruption:* PRO significantly lower numbers of MRI pause due to body movements (PRO: 0.22±0.42; DEX: 0.81±1.06; *P* < 0.001) ○ *Technique failure*: Only 1/49 PRO patients compared to15/46 DEX patients (*P* < 0.001) ○ *PAED*: Total score was significantly less in PRO than in DEX at both 5 and 10 min assessment (*P* < 0.01) ○ *Parental satisfaction*: On first post-operative, parents of children receiving PRO significantly more satisfied than parents of children receiving DEX (PRO: 9.5±0.8; DEX: 8.9±1.6; *P* = 0.039) • *Safety:* ○ No severe adverse events observed. ○ Desaturation (SpO_2 85-92%): Two brief and mild episodes of desaturation in children receiving PRO	"For long-duration MRI in children, PRO technique delivered a higher-quality care than DEX technique in terms of timeliness, effectiveness, and parental satisfaction. Both PRO and DEX techniques can be safely administered in pediatric MRI. The hemodynamic profile of PRO and DEX differed although these differences were within normal range for anesthetized children" (p. 818)
Hijazi, 2014,[21] Saudia Arabia	• 292 procedures (in 275 patients) in which six were subsequently removed due to incomplete data collection (144 CH vs. 142 MDZ) • *Clinical efficacy:* ○ *Time*: CH significantly shorter than MDZ with respect to time to achieve sedation (*P* < 0.001) and time to recovery (*P* = 0.0386) and longer with respect to sedation duration (*P* <0.01) ○ *Successful sedation:* 16% of CH patients vs. 74.3% of MDZ patients not sufficiently sedated at 30 minutes after first dose (*P* = 0.0001). Successful higher in CH group (94.9%) than MDZ group (62%) (*P* = 0.0001). Generally, patients who required a second dose of study drug were older and heavier. ○ Significant interaction between time and drugs as, although no differences at baseline, CH had higher degree of sedation than MDZ at 15, 30, 45 and 60 minutes. No differences were observed at 75 and 90 minutes. This indicates that children receiving CH had a higher degree of sedation at a faster rate than MDZ. • *Safety:* ○ No major adverse events observed. ○ Paradoxical agitation: No events in CH arm but 8 events in MDZ arm (*P* = 0.0039) ○ Mean arterial BP ≥25% of baseline: Four events in CH arm but no events in MDZ arm (*P* = 0.046)	"CH compared to MDZ, had a shorter time to achieve sedation, a higher success rate, less need for a second dose, and decreased the time spent in the day care unit. Older and heavier patients are more likely to require a second dose of the study drug to be sedated." (p. 123)
Pedersen, 2013,[16] Denmark	• 120 patients (60 per treatment group) • *Clinical efficacy:* ○ *Time to discharge:* average time for discharge from recovery room was significantly shorter for PRO (63 mins, range: 55 to 75) than sevoflurane (71 mins,	"neither of the two methods used in the present study were without drawbacks. The relatively low dose of

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	range: 16 to 213). At 90 mins, 10 children on PRO were undischarged while 24 children on sevoflurane were undischarged (*P* =0.008) ○ *Quality of scan:* 15 children in PRO moved during scan while none in sevoflurane group moved (*P* < 0.001). 14 of these children required further induction with thiopental. In total, eight children in PRO group and 12 children in sevoflurane group required increase in infusion rate and sevoflurane concentration as vital parameters indicated that anesthesia was not deep enough. ○ *PAED scale*: Scores at 15 and 30 minutes were lower for children receiving PRO than sevoflurane (*P* < 0.01) ○ *Parental satisfaction:* No treatment-group difference in parental satisfaction with stay in recovery room and induction	PRO-remifentanil infusion ensured a satisfactory stay in the recovery room, but additional bolus doses of PRO were necessary during the MRI in some of the children because of movement. Sevoflurane was reliable during the MRI; however, a few children had a tendency to respiratory depression, and postoperatively emergence delirium was a concern." (p.994)
Demir, 2012,[20] Turkey	• 100 patients (50 per treatment group) • *Clinical efficacy:* ○ *Recovery time:* Statistically lower in multiphase sedation group (21.06±6.58 min) than in control group (26.35±8.07 min) (*P* = 0.001) ○ *STA-I scores:* After procedure, parents in multiphase sedation group was less anxious with STA-I scores lower (41.36 ± 8.23) than in control group (48.07 ± 9.1) (*P* = 0.001) ○ *Parental satisfaction*: Higher in multiphase group (80.92 ± 19.57) than in control group (72.84 ± 18.27) (*P* = 0.035) ○ *Number of IV attempts*: Both number of IV access attempts and time of stay in preparation room lower in multiphase sedation group (*P* = 0.001) ○ *Additional PRO:* Multiphase sedation required less PRO(1.36 ±1.11 mg kg^{-1}) to achieve deep sedation than in control group (2.47 ± 0.67 mg kg^{-1})	"'Multiphase sedation' procedure provides children to feel less pain and anxiety, and decreases parental anxiety while increasing their satisfaction. It supplies a comfortable and safe sedation, as it provides a short and problem-free preparation process for the attending anesthetist as well." (p. 511)
Fallah, 2012,[14] Iran	• 60 patients (30 per treatment group) • *Clinical efficacy:* ○ *Ramsay sedation score:* A score of 4 achieved in 40% of children receiving MDZ while 93.3% of children in CH (*P* < 0.001) ○ *Completion of CT scan:* Successfully completed in 40% (95% CI: 0.23 to 0.57) in MDZ but 76.7% (95% CI: 0.62 to 0.92) in CH (*P* < 0.05) ○ No statistical differences in total and procedure time. • *Safety:* ○ *Mild AE*: 10% children in CH and 3.3% of children in MDZ	"Oral CH was more effective than intranasal MDZ in sedation induction in uncooperative children undergoing CT scan" (p.234)
Brecelj, 2011,[13] Slovenia	• 201 patients (97 MDZ-KET vs. 104 KET) • *Clinical efficacy:* ○ *Supplemental KET doses*: In patients in MDZ-KET arm, 57% received one and 5% received two supplemental doses of KET (0.25 mg kg^{-1}). In patients in KET arm, 69% received one and 10% received two additional KET doses (*P* > 0.05) ○ *Appropriateness of sedation*: Endoscopy team rated sedation as optimal / acceptable in 96% of patients in MDZ-KET and 99% of patients receiving KET (*P* > 0.05)	"The sedation protocol with KET is safe and efficient. The starting dose of KET should be at least 1 mg/kg. There is an advantage to the use of MDZ as premedication before KET in paediatric patients because the frequency of emergence reactions in hospital was

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	• *Safety:* ○ *Emergence reactions*: Occurred in four patients on MDZ-KET and 13 patients receiving KET (*P* = 0.02) ○ Majority of adverse reactions were short-term without any later implications. They were balanced between the two groups including laryngospasm, profound salivation and need for additional oxygen.	reduced compared with sole KET use." (p. 748)
Jain, 2010,[11] India	• 99 patients (29 MDZ vs. 31 MDZ-KET vs. 32 placebo) • *Clinical efficacy:* ○ *Number of patients crying during venipuncture:* Higher prevalence in placebo group than active-treatment group (RR 2.37, 95% CI: 1.55 to 3.63). ○ *Sedation score*: Significantly more patients in placebo group were crying or displayed anxiety than other two groups at all time intervals outside of baseline (*P* < 0.05) ○ *Venipuncture scores:* Significantly more patients in placebo with score 3 or 4 than patients in active treatment group. Active treatment groups were comparable. ○ *Venipuncture attempts*: Comparable between treatment groups ○ *Movement:* No child in MDZ-KET moved during the scan, whereas 14/30 patients moved in placebo group and 5/29 patients in MDZ group (*P* < 0.001). Motion artifacts reported by radiologist in 6/30 and 2/29 children in placebo and MDZ group (*P*< 0.001). None required a repeat scan. ○ *Mean dose of KET required:* Comparable among the groups (MDZ: 1.2 ± 0.32; MDZ+KET: 1.12 ± 0.4; placebo: 1.3 ± 0.54 mg kg^{-1}) ○ *Parental satisfaction*: Fewer parents of patients receiving placebo (9%) rated satisfaction as excellent than parents of children receiving MDZ (62%) and MDZ+KET (81%) (*P* < 0.01) ○ Immediate post procedure sedation scores and mean duration to discharge were comparable between three groups • *Safety:* ○ None of the children had any complication during or post procedure.	"A low-dose combination of oral MDZ and KET or oral MDZ alone effectively reduces the stress during i.v. cannulation in children undergoing CT imaging without any adverse effects. However, the combination provides more children in calm and quiet state when compared to MDZ alone at venipuncture." (p. 330)
Observational Studies: Pediatrics		
Teshome, 2014,[23] USA	• 281 sedations in which 10 patients had incomplete documentation and 5 patients had failed sedation (154 pentobarbital vs. 112 DEX) • *Clinical efficacy:* ○ *Induction time*: Similar between groups ○ *Time*: DEX associated with shorter recovery time (39 ± 21 min) than pentobarbital (49 ± 27 min) (*P* = 0.002) and total sedation time (DEX: 107 ± 28 min vs pentobarbital: 157 ± 44 min, *P* = 0.0001) ○ 45% of patients in pentobarbital group and 40% from DEX group received an additional 1 to 2 mg/dose IV midazolam. • *Safety:* ○ *All adverse events:* 4.5% (n=7) in pentobarbital and 0.9% (n=1) in DEX reported an AE (*P* = 0.08)	"DEX and pentobarbital can both be used successfully for MRI sedation in children. However, DEX had a significantly shorter recovery time and total sedation time in our population"

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	○ Most common adverse events in pentobarbital group was emergence delirium (n= 4/7) and oxygen desaturation (n=2/7). The only adverse event observed in DEX group was oxygen desaturation	
Sebe 2013,[24] Turkey	• 200 patients (100 PRO vs. 100 MDZ) • *Clinical efficacy:* ○ *Time*: Average sedation period shorter with PRO (44 ± 9 min) than with MDZ (52.5 ± 14.3 min). Average length of stay in emergency room was 20.70 ± 5.94 min in PRO arm and 41.77 ± 11.6 min in MDZ arm (P = 0.01 for both outcomes). Patients receiving PRO reached appropriate sedation level in shorter period than MDZ (PRO: 2.0 ± 0.9 min vs. MDZ: 7.0 ± 6.3 min, P = 0.01) ○ *Ramsay sedation scale*: score significantly higher in PRO group than MDZ group (P = 0.001) ○ *Additional drug dose*: No patients in PRO group required additional drug dose beyond what was indicated in the defined protocol. 10% in MDZ group required an additional dose of MDZ (P = 0.01) • *Safety:* ○ Nausea was the only drug-related AE noted, observed in two patients in MDZ group.	"PRO seems to be more effective, achieve the appropriate sedation level more quickly, and provide a faster onset of sedation than midazolam in pediatric procedural sedation and analgesia. PRO is preferred for imaging studies (CT and MRI) to reduce occurrence of undesired motion artefacts. Although both drugs are safe to use for sedation before pediatric imaging procedures, PRO is preferred with appropriate preparation"
Clinical practice guidelines		
NICE. Sedation in children and young people. 2010,[25] UK	• Treatment and care should consider patients' needs and preferences • Pre-sedation assessment should be conducted and documented to establish suitability for sedation (based on factors including medical condition, weight, past medical problems, current and previous medications, physical status, psychological and developmental status). Seek advice from specialist before delivering sedation if there are concerns about potential airway or breathing problems, a child is assessed as ASA > grade 3 or in infants/neonates • Patient, or those with consent authority, should provide informed consent and documented • No drugs have a UK market authorization for sedation in infants, children and young people under 19 ○ Physicians should use a drug summary of product characteristics and the British National Formulary for children to inform choice for the individual patient • Both a healthcare professional and assistant trained in delivering and monitoring sedation in children and immediate access to resuscitation and monitoring equipment should be made available • Healthcare professional delivering sedation should have knowledge, understanding, up-to-date competency and experience in assessing, effectively delivering sedatives, monitoring patients, providing recovery care and managing complications. Extent of life support skills depends on the levels of sedation. • In patients under deep sedation, several clinical factors must be continuously monitored and interpreted including depth of sedation, respiration, oxygen saturation, heart	

First Author, Publication Year, Country	Main Study Findings	Authors' Conclusions
	rate, etc… • Research recommendations provided for key areas in pre-sedation assessment, personnel training, drug combination and the development of a national registry of sedation.	

AE = adverse events; CH = chloral hydrate; CI = confidence interval; CPG = clinical practice guidelines; CT = computed tomography; DEX = dexmedetomidine; ERCP = endoscopic retrograde cholandiopancreatography; IV = intravenous; KET = ketamine; MA = meta-analysis; MD = mean difference; MDZ = midazolam; min= minute; MR = magnetic resonance; MRI = magnetic resonance imaging; OR= odds ratio; *P* = probability value; PAED = Pediatric anesthesia emergence delirium scale; PRO = propofol; RCT = randomized controlled trial; RD = risk difference; s= seconds; SR = systematic review; UK = United Kingdom; USA = United States of America; VAS = visual analog scale; vs. = versus; WMD = weighted mean difference