Remifentanil for procedural sedation: a systematic review of the literature

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ABSTRACT

Objective We sought to determine the performance characteristics of remifentanil as an agent of procedural sedation and analgesia (PSA) for adult and paediatric patients undergoing procedures similar to those executed in the ED.

Methods We systematically reviewed electronically published literature, grey literature, conference proceedings and trial registries from 1946 to 2015. Outcome measures included PSA effectiveness, recovery time, patient safety and resource management. We performed narrative summary analyses. Heterogeneity among selected studies precluded meta-analysis.

Results We found 1525 citations, reviewed 34 full manuscripts (kappa=0.64) and included 10 studies (kappa=0.71). Seven were randomised controlled trials and three studies took place in the ED. Included procedures were lumbar puncture (80), cardioversion (66), orthopaedic manipulation (63), incision and drainage (15), thoracostomy (8) and nasal packing (2). There was extensive variation in remifentanil dosing (0.15– 1.5 µg/kg), administration protocols and use of additional PSA drugs. All studies noted superior or equivalent sedation effectiveness compared withcontrols. Several studies, including all those performed in the ED, noted faster procedure completion or patient recovery with remifentanil compared with control groups. The most commonly reported adverse event was respiratory depression, especially in paediatric patients. All studies were found to carry significant risk of bias.

Conclusions There is currently a lack of high-quality data on the use of remifentanil in the ED. Physicians should exert caution when using remifentanil in the absence of published standardised dosing protocols in light of frequently reported paediatric respiratory depression. However, PSA efficacy combined with faster recovery times merit ongoing investigations into its use.

What this paper adds

What is already known on this subject

- Remifentanil, a short-acting synthetic opioid, possesses several unique properties that render it attractive as a novel procedural sedation (PSA) drug. Despite its widespread use in monitored anaesthetic care, the suitability of remifentanil for use in the ED has not been proven. We sought to summarise the existing knowledge on the efficacy and safety of its use in patients undergoing PSA in an ED or similar setting.

What this study adds

- Our review shows that remifentanil provides satisfactory PSA conditions for the performance of common ED procedures and expedites recovery and discharge time when compared with other commonly used PSA agents. However, physicians should exert caution when using remifentanil due to the absence of ED-specific dosing protocols and the increased risk of respiratory depression observed in paediatric patients.

INTRODUCTION

The delivery of procedural sedation and analgesia (PSA) is fundamental to the practice of emergency medicine.[1–6] Many conditions encountered in the ED require patients to undergo unpleasant diagnostic and therapeutic procedures and PSA allows these interventions to be completed safely and quickly while minimising patient distress. Most current PSA agents have well-documented central nervous system (CNS), respiratory and cardiovascular side effects.[6–8] The 'ideal' PSA agent provides analgesia and anxiolysis, is short-acting, avoids respiratory depression and is haemodynamically inert. In the search for this ideal PSA agent, drugs traditionally thought to be suitable only for the operating room have proven to be useful to the emergency physician. For example, propofol is safe and efficacious in both adult and paediatric ED PSA.[9–11] Hence, as novel short-acting sedatives and analgesics are introduced into practice, it is important to evaluate their fitness for use in the ED.

Remifentanil is a synthetic short-acting opioid widely used by anaesthetists for awake airway manipulation, for the induction and maintenance of general anaesthesia and for sedation during ambulatory procedures.[12 13] It possesses several unique properties that render it attractive as a novel PSA agent. It provides rapid deep analgesia with minimal CNS depression and importantly, it is metabolised by esterases and does not depend on hepatic or renal function for elimination. Consequently, its half-life remains short (3–8 min) regardless of extremes of patient age, comorbidities, or the duration of its infusion.[13–15]

We sought to summarise the existing knowledge of the use of remifentanil for PSA of patients undergoing common emergent procedures in an ED or similar setting. By conducting a systematic review, we aimed to compare the performance of remifentanil, by itself or in conjunction with other drugs, to commonly employed PSA medications. Specifically, our outcome measures included: (1) PSA efficacy (2) PSA duration (3) patient safety and (4) resource utilisation.

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MATERIALS AND METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16]

Search strategy

With the assistance of an expert research librarian, we designed a comprehensive electronic search strategy. We originally searched MEDLINE (Ovid) (1946 September 2013), PubMed (1967 September 2013) and EMBASE (1947 September 2013) and repeated the electronic search in December 2015 to look for new relevant publications. We did not restrict our search by year, language or publication status (see online supplementary file).

We searched the National Institute of Health Trial Registry, the Cochrane Central Registry of Controlled Trials and the International Standard Randomized Controlled Trial Number Register for any ongoing trials. We hand-searched abstracts from the American College of Emergency Physicians Scientific Assembly (2011–2012), the Society of Academic Emergency Medicine Annual Meeting (2011–2012), the Canadian Association of Emergency Physicians Conference (2011–2012), the International Conference of Emergency Physicians (2010–2012), the American Society of Anesthesia Annual Meeting (2011–2012) and the Canadian Anesthesiologists' Society Annual Meeting (2011–2012). We also contacted the authors of prominent studies to identify any ongoing trials or unpublished reports. Finally, we examined the bibliographies of retrieved articles for any citations that could have been missed by the electronic search strategy.

Selection of studies

To be included in this review, studies had to meet the following criteria: (1) human study; (2) remifentanil used in PSA; (3) assessment of at least one of the predetermined outcomes; and (4) ED or similar setting (ie, procedure rooms with ED-equivalent resources). Studies set in the operating room or intensive care unit (ICU) were excluded as we felt they were not equivalent to the ED environment. We excluded review articles, opinions or letters to the editor. In order to properly capture respiratory depression as an important adverse event, we also excluded procedures on intubated patients or studies in which intubation was performed as part of the procedure.

Two reviewers (MK, HR) independently screened titles and abstracts in the initial selection process. We subsequently retrieved all full-text manuscripts for which a citation was deemed potentially relevant by at least one reviewer or if a decision could not be made based on title and abstract alone. The same two reviewers then used a set of a priori criteria to independently select studies for final inclusion. If eligibility remained unclear after full-text review, the corresponding author was contacted for clarification before reaching a final decision by consensus. We calculated inter-rater agreement using kappa statistics at each selection stage.

Data abstraction

Two reviewers (MK, HR) abstracted data independently using a standardised and piloted data collection tool. The data collected included publication status, year, country and language of publication, study design, setting, population characteristics, the PSA regimen used and the procedures performed. The outcomes recorded were PSA effectiveness (sedation effectiveness, patient and physician satisfaction and procedural success), PSA duration and time to discharge, patient safety (oversedation, respiratory depression, cardiovascular instability, nausea/vomiting and death) and resource utilisation. Outcomes were defined and documented in the same manner as they were originally measured in the protocols of the selected study.

Data synthesis and quality assessment

Clinical heterogeneity among studies precluded meta-analysis. Instead, we performed narrative summary analyses of predefined outcome measures. If a study did not report on a particular outcome, we assumed it had not been measured and excluded the study from analysis of that outcome.

We explored the quality of selected randomised controlled trials (RCTs) using the Cochrane Collaboration's tool for assessing risk of bias.[17 18] This tool requires the evaluation of six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. We judged each domain to contain a low, unclear or high risk of bias. We weighted the importance of risk of bias in each domain according to the clinical context and appraised the overall risk for each study. We summarised the risk of bias in each domain for all included studies and narratively appraised the validity of individual studies.

RESULTS

Literature search results and study characteristics

Our search strategy identified 1525 potentially relevant citations, 1519 from electronic databases and 6 from grey literature. After screening titles and abstracts, we retrieved 34 manuscripts for full-text review (kappa=0.64, 95% CI 0.44 to 0.84) and selected 10 studies for inclusion based on our predetermined selection criteria (kappa=0.71, 95% CI 0.47 to 0.95). Four authors were contacted to clarify the setting of their study, as this was the chief reason for reviewer discordance. Figure 1 summarises study selection.

Key characteristics of included studies are listed in tables 1 and 2. In total, 151 adults and 428 children who underwent 616 procedures were included. There was significant inter-study variation in patient characteristics, the types of procedures performed, the dosing of remifentanil and of co-medications and the way in which sedation was measured (table 3).

No two protocols administered remifentanil using the same regimen. There was marked variability in the total dose of remifentanil dispensed across all studies. In fact, several trials sought to determine the optimal dose of remifentanil, alone or in combination with other PSA drugs.[19–21] Three studies used only remifentanil for PSA,[19 22 23] while the rest combined it with other agent(s). The most commonly coadministered medication was propofol.[19–21 24–28] Three studies premedicated patients with benzodiazepines prior to procedure onset.[22 23 25]

Quality of included studies

The results of this analysis are summarised in figure 2. Most RCTs were found to be at unclear or significant risk of bias. In examining performance bias, only three studies blinded outcome assessors[21 26 27] and only one blinded participants and personnel.[27] Two studies were at significant risk of attrition bias for not adhering to intention to treat analysis. Bauman excluded 27/202 patients after randomisation because of intravenous access or infusion pump failure.[20] Keidan excluded 3/80 patients for receiving non-protocol drugs during PSA.[26] No study was at high risk of selective reporting but certain outcomes were under-reported resulting in an unclear risk of bias. One trial did not specify cardiovascular parameters between groups and instead simply stated that they were not statistically significant.[19]

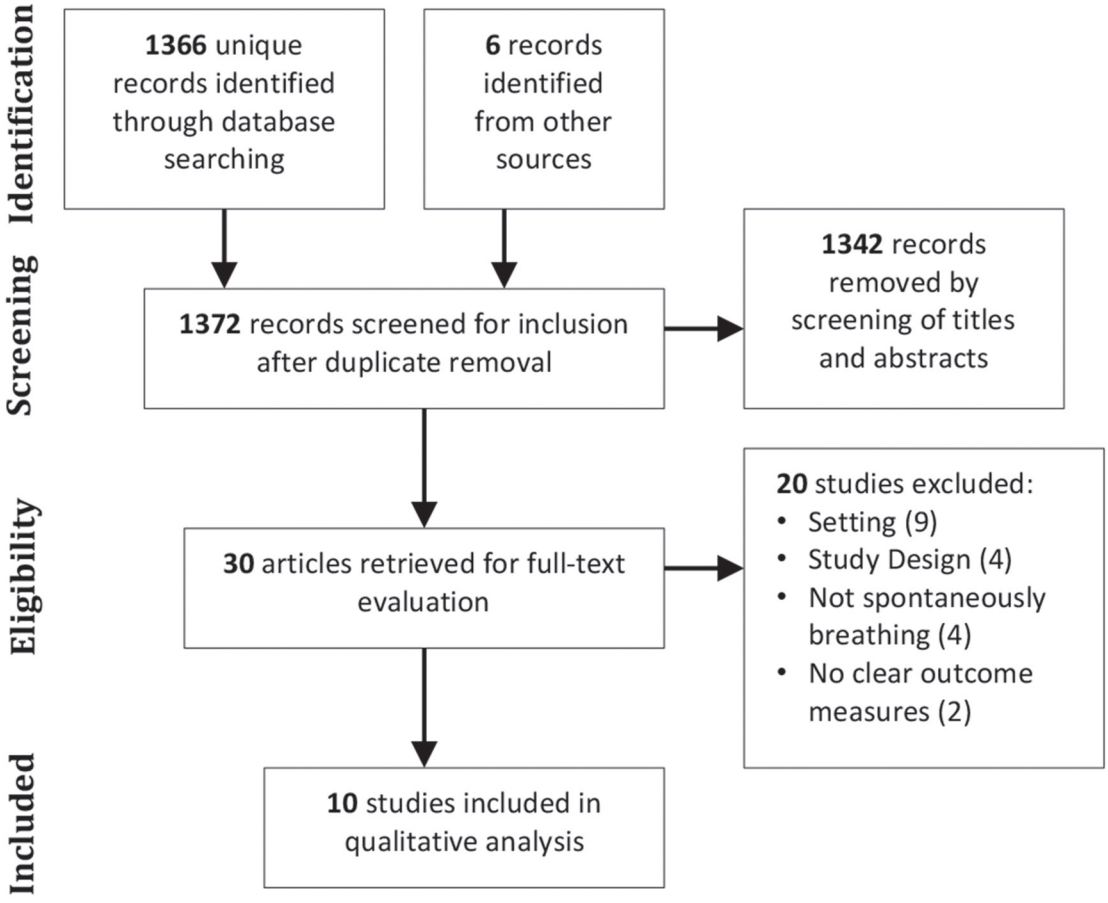

Figure 1 Flow diagram of the study selection process.

Another RCT did not provide the absolute values of PSA duration, only that the experimental and control groups significantly differed.[25] Lastly, one study was at high risk of bias because of patient crossover. Among 40 patients sedated with either remifentanil-propofol or morphine-midazolam, three patients in the remifentanil group and two in the control group received narcotic pre-medication prior to randomisation. Furthermore, two patients in the remifentanil group actually received morphine-midazolam.[24]

Table 1 Characteristics of included studies

Characteristic	Studies, n(%)=10
Median year of publication (range)	2006 (1999–2015)
Country of publication	
USA	3 (30)
Turkey	3 (30)
UK	2(20)
Israel	1(10)
Canada	1(10)
Language	
English	10 (100)
Study design	
Randomised control trial	7 (70)
Prospective cohort	1(10)
Case series	1(10)
Health records review	1(10)
Setting	
Clinic/procedure room	5 (50)
ED	3 (30)
Cardioversion suite	1(10)
Unspecified*	1(10)

* Study set in 'an area with standardised emergency equipment'. Correspondence with the author of this study confirmed that the 'area' was not within an operative suite or intensive care setting.

Table 2 Summary of patients and procedures performed across all studies

Characteristic	Number (%)
Population	579 (100.0)
Adult	151 (26.1)
Paediatric*	428 (73.9)
Procedures performed	616 (100.0)
Bone marrow aspiration	105 (17.0)
Bone marrow biopsy	98 (15.9)
Lumbar puncture	80 (13.0)
Cardioversion	66 (10.7)
Orthopaedic manipulation	63 (10.2)
Incision and drainage	13 (2.1)
Tube thoracostomy	8 (1.3)
Renal biopsy	4 (0.6)
Posterior nasal packing	2 (0.3)
Peritonsillar abscess drainage	2 (0.3)
Unspecified	175 (28.4)

* 465 paediatric sedations were performed in total

Table 3 General description of 10 included studies

Author, year	Country	Study design	Setting	Population	Procedure	Study protocol	Assessment of sedation	Emergence from PSA and discharge criteria	Additional information
Antmen 2005[19]	Turkey	Unblinded, single centre, RCT	'Area with standard emergency equipment'	80 children (5–16 years)	BMA	Remifentanil (1 µg/kg) vs alfentanil (20 µg/kg) vs midazolam 0.05 µg/kg and remifentanil (0.5 µg/kg) vs midazolam 0.05 µg/kg and alfentanil (20 µg/kg)	Sedation graded as: (0) awake, (1) drowsy (2) asleep (deep sedation) *Note: No patient had a Sedation Score >1.*	Not specified	
Bauman 2002[20]	USA	Unblinded, single centre, RCT	'Small room near ICU'	175 children (52 weeks–12 years) excluded if cardiovascular unstable, difficult airway, not fasted	'Any painful procedure lasting <30 min'	Remifentanil at three different doses (0.53 µg/kg, 0.8 µg/kg, 1.1 µg/kg bolus then 1 µg/kg/min, 1.5 µg/kg/min or 2.0 µg/kg/min infusion, respectively) and methohexital 0.8 mg/kg then 0.15 mg/kg/min vs fentanyl 1 µg/kg, 1.5 µg/kg or 3 µg/kg then propofol 2 mg/kg bolus followed by 0.18 mg/kg/min infusion	Patient movements and the need for additional sedation boluses	End of sedation: time to first movement and eye opening. Discharge criteria: Aldrete Score >10	27 patients excluded post randomisation because of pump/infusion Failure
Dunn 2010[24]	UK	Unblinded, single centre, RCT	ED	40 adults (16–65 years) ASA ≤2	Anterior GH dislocation reduction	Remifentanil 0.5 µg/kg and propofol 0.5 mg/kg then remifentanil 0.5 µg/kg or propofol 0.25 mg/kg PRN vs morphine titrated up to 0.5 mg/kg and midazolam 1 mg every 3 min titrated up to 0.15 mg/kg	Observer Assessment of Alertness/Sedation Score	Discharge criteria: 'usual departmental criteria'. Patients had to be alert, oriented, walking independently and tolerating PO intake	5 patients received analgesic premedication
Hayes 2008[21]	Canada	Double blind, single centre, RCT	Haem-onc clinic	34 children, ASA ≤3, excluded obese and difficult airway	LP	Remifentanil 1.5 µg/kg and propofol 2 mg/kg vs remifentanil 0.5 µg/kg + propofol 4 mg/kg	Patient movements used to determine minimal effective dose	End of Sedation: numerical scale. Discharge criteria: not specified	
Ince 2013[25]	Turkey	Unblinded, single centre, RCT	Haem-onc clinic	29 children (2–18 years, fasted, ASA ≤3) were sedated for 60 procedures	LP, BMA, bx, intrathecal chemotherapy	Remifentanil 0.5 µg/kg and propofol 2 mg/kg vs fentanyl 0.5 µg/kg and propofol 2 mg/kg	patient movements	End of sedation: time to eye opening. Discharge criteria: modified Aldrete Score >9	All patients were premedicated with midazolam 0.05 mg/kg
Keidan 2001[26]	Israel	Single centre RCT, blinded data collector	Haem-onc clinic	80 children, ASA=3	Bone marrow bx	Remifentanil 0.15 µg/kg then 0.1 µg/kg/min and propofol 3 mg/kg then 300 µg/kg/min vs propofol 3 mg/kg then 300 µg/kg/min	Patient movements	End of sedation: time to eye opening. Discharge criteria: Aldrete Score >8	

Continued

Table 3 Continued

Author, year	Country	Study design	Setting	Population	Procedure	Study protocol	Assessment of sedation	Emergence from PSA and discharge criteria	Additional information
Malpete 2006[27]	Turkey	Double blind, single centre RCT	Cardioversion suite	63 adults, excluded ASA >3, BMI >35, potentially difficult airway	Cardioversion	Remifentanil 0.25 µg/kg and propofol 1 mg/s to desired sedation (mean dose propofol 0.90 mg/kg) vs fentanyl 1 µg/kg and propofol 1 mg/s until desired sedation (mean dose propofol 0.88 mg/kg)	Ramsey sedation score *Note: PSA administered till score of 5 reached then all drug infusions were stopped*	End of sedation: Time to eye opening, to clear speech, and to sitting up. Discharge criteria: not specified	
Dunn 2006[28]	UK	Case series	ED	11 adults (16–65 years) ASA ≤2	Anterior GH dislocation reduction	Remifentanil 0.5 µg/kg then 0.25 µg/kg PRN and propofol 0.5 mg/kg and 0.25 mg/kg PRN	No specific assessment criteria. All patients remained verbally responsive throughout.	End of sedation: patient being 'clinically alert'. Discharge criteria: criteria not specified	2 patients premedicated with glycopyrrolate
Litman 1999[22]	USA	Prospective cohort	Haem-onc clinic	17 children (2–12 years) sedated for 20 procedures excluded not fasted, obese, difficult airway	LP, BMA, renal bx, fracture reduction	Remifentanil 1 µg/kg bolus then 0.1 µg/kg/min infusion, doubled every5 min till desired effect.	AAP Sedation Scale *Note: Infusion doubled until AAP Score 3 was reached, the patient was apnoeic or unresponsive to verbal or painful stimuli.*	discharge criteria: aldrete score >10	All patients premedicated with midazolam 0.05 mg/kg and odansetron 2 mg
Sacchetti 2011[23]	USA	Health records review	ED	37 adults; 13 children (16 months–74 years)	I&D, LP, cardioversion, tube thoracostomy, nasal packing, orthopaedic manipulation	Remifentanil 0.16 µg/kg/min infusion	Not specified	Not specified	Four patients premedicated with lorazepam 0.5 mg

Notes: Studies performed in the ED have been bolded.

ASA, American Society of Anaesthesia; BMA, bone marrow aspiration; bx, biopsy; CCU, coronary care unit; GH, glenohumeral; haem-onc, haematology-oncology; ICU, intensive care unit; I&D, incision and drainage; LP, lumbar puncture; RCT, randomised control trial, PRN, as needed; PO, by mouth.

Main results

The following sections present narrative summaries for each outcome measure. Figure 3 summarises which studies measured which outcome.

PSA effectiveness

Remifentanil provided satisfactory PSA conditions and did not alter procedural success in 9 of 10 studies. In the only ED RCT, 40 adults underwent anterior shoulder reduction using either remifentanil-propofol or midazolam-morphine PSA. Physicians rated reduction conditions on an ordinal scale and patients reported pain numerically during PSA. Physician and patient satisfaction was the same with either sedation regimen. Reduction conditions were predominately rated as 'adequate, good or excellent' and most patients experienced little to no pain.[24] In an ED case series by the same authors, remifentanil-propofol PSA resulted in 11 successful shoulder reductions with minimal pain and either 'very satisfactory' or 'satisfactory' patient experience.[28] A separate ED health records review of 37 adults and 13 children who underwent remifentanil-only PSA reported efficacious completion of several common procedures. However, 12 patients in this study required an additional anxiolytic.[23]

A paediatric study of 80 patients undergoing bone marrow biopsy found equivalent patient and parental satisfaction, superior procedural conditions and less use of rescue sedation when comparing remifentanil-propofol to propofol alone.[26] Another study compared remifentanil-midazolam and remifentanil alone to alfentanyl-midazolam and alfentanyl alone in 80 children undergoing bone marrow aspiration. Adequate sedation was obtained in all groups. Superior pain control, as measured by a visual analogue scale, occurred with remifentanil in comparison to alfentanyl alone.[19]

Sedation with remifentanil-propofol was compared with fentanyl-propofol in 63 adult cardioversions[27] and in 29 children undergoing 60 procedures.[25] In both of these RCTs, there was no difference in procedural success or sedation effectiveness. Cardioversion patients did not voice any complaints when evaluating their sedation experience with either PSA regimen.[27]

When different doses of remifentanil-methohexital were compared with fentanyl-propofol in 175 children undergoing painful procedures, sedation effectiveness did not differ between groups.[20]

The one study that reported unsatisfactory PSA was a prospective cohort of 17 paediatric outpatients pretreated with

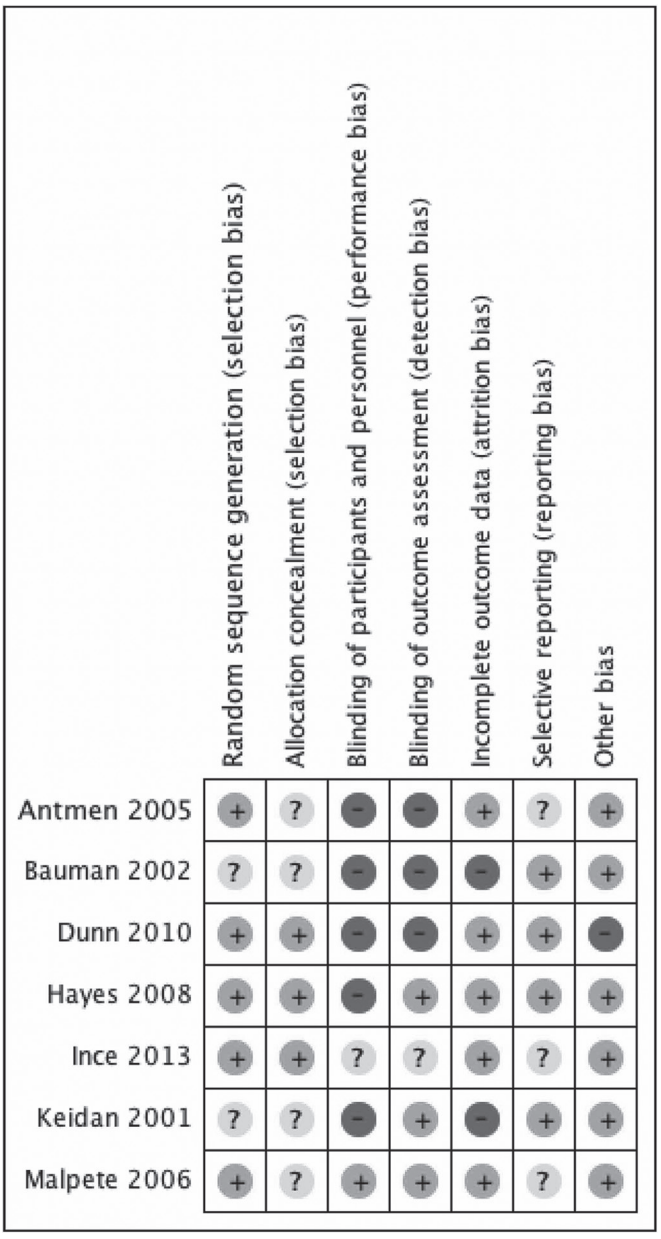

Figure 2 Risk of bias across all seven randomised control trials as assessed by the Cochrane risk of bias tool.

midazolam and then sedated with remifentanil for 20 painful procedures.[22] Three children experienced anxiety, requiring cessation of remifentanil and rescue with either propofol or ketamine.

Lastly, Hayes[21] used the 'absence of interfering movement' to find the minimum effective dose of remifentanil coadministered with either 2.0 mg/kg or 4.0 mg/kg of propofol. Effective sedation was achieved in both groups in the dose-finding portion of this study.

PSA duration

Faster recovery or discharge occurred in the five of six RCTs that compared remifentanil to other PSA agent(s).[20 24-27] An ED RCT found median recovery time after remifentanil-propofol PSA was 15 min (95% CI 15 to 20) compared with 45 min (95% CI 20 to 48) with morphine-midazolam. All remifentanil-propofol patients had fully recovered by 30 min compared with 90 min, with morphine-midazolam. When remifentanil-propofol was compared with fentanyl-propofol for 60 paediatric procedures, PSA duration remained unchanged while recovery was significantly faster with remifentanil-propofol ($p < 0.02$). Discharge time was also shorter, but not statistically significant.[25] Children sedated with remifentanil-propofol for BMA were 'home ready' faster than with propofol alone (33±15 min vs 52±24 min, $p < 0.001$).[26] When remifentanil-propofol was compared with fentanyl-propofol for 63 adult cardioversions, time to adequate sedation was unchanged while recovery time was significantly shorter with remifentanil-propofol (412±90s vs 511±126s; $p < 0.002$).[27]

One RCT determined the minimum effective dose of remifentanil coadministered with 2.0 mg/kg or 4.0 mg/kg of propofol. Procedure duration was the same in both groups but recovery time was halved with 1.5 μg/kg of remifentanil with 2.0 mg/kg of propofol compared with 0.5 μg/kg of remifentanil with 4.0 mg/kg of propofol (median awakening time: 10 vs 22 min).[21]

In a review of 37 patients undergoing remifentanil-only ED PSA, time from infusion termination to recovery was 'generally 5 min'.[23] In an ED case series of 11 adults mean recovery time was 3 min (range: 1–6 min).[28] Lastly, in 20 paediatric outpatients premedicated with midazolam then sedated with remifentanil, the mean time to discharge readiness was 9.5±4.3 min.[22]

Patient safety

No complications occurred in studies set in the ED.[23 24 28] Across all studies, the most frequent adverse event was respiratory depression. One adult RCT reported an insignificant increase in brief apnoea, resolved with verbal stimulation alone, when sedation with remifentanil-propofol was compared with fentanyl-propofol (17% vs 6%, $p=0.24$).[27] In a trial of 175 children, 20% more respiratory events requiring 'more than head repositioning' occurred with remifentanil-methohexital compared with fentanyl-propofol (54% vs 34%, $p<0.02$). This effect was largest in patients who received the highest dose of remifentanil.[20] Likewise, children sedated with remifentanil-propofol had 9% more hypopnoea (20% vs 11%; $p<0.05$) requiring positive pressure ventilation (PPV) compared with propofol alone.[26]

Four of 17 children pretreated with midazolam and sedated with remifentanil desaturated (SpO_2: 83%–89%) but recovered quickly with gentle stimulation. An additional ten children had periods of apnoea that required prompting to breathe.[22] One child became anxious, unresponsive and hypoxaemic necessitating rescue sedation and PPV.

When two paediatric dosing regimens of remifentanil-propofol (remifentanil 1.5 μg/kg/propofol 2 mg/kg vs remifentanil 0.5 μg/kg/propofol 4 mg/kg) were compared, apnoea occurred in 88% of patients with a majority requiring intermittent PPV in both groups. Although the incidence of apnoea was the same, duration of apnoea was greater in patients receiving higher dose remifentanil (mean: 110 s, range: 0–228 s vs mean: 73 s, range: 0–110 s, $p<0.05$).[21]

Several paediatric studies noted an insignificant trend of decreased HR and blood pressure.[21 25 26] One reported a statistically significant decrease in diastolic pressure when comparing remifentanil-propofol and fentanyl-propofol.[25] No intervention was required. There were no cases of intubation, vomiting, aspiration, oversedation not marked by respiratory depression, hospital admissions or death related to PSA.[19–22 24 26 27]

Resource utilisation

Not reported in any study.

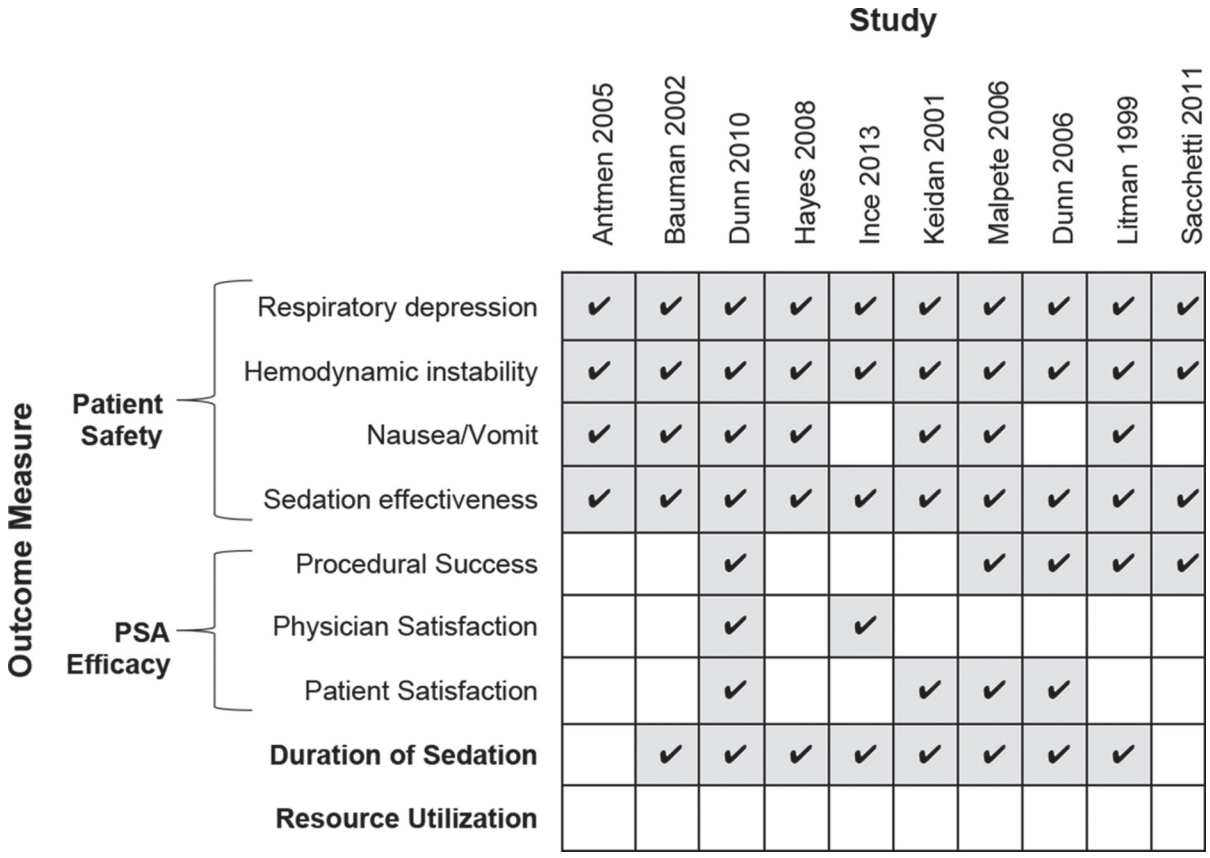

Figure 3 Prespecified outcomes measured by selected studies.

DISCUSSION

Limitations

There are several potential limitations to this review. First, despite an exhaustive search of the literature only 10 pertinent studies were found and only 3 of these took place in the ED. PSA was delivered by emergency physicians in two of these,[23 24] while in the third,[28] sedations were done by both anaesthetists and emergentologists. When specified, PSA providers outside of the ED were anaesthetists.[19 21 27]

All studies were identified as being at high or unknown risk of bias in at least one prespecified domain. The relative paucity of available data, especially high-quality data, highlights the limited strength of conclusions that can be drawn from the existing literature.

It was not possible to combine results quantitatively because of considerable clinical heterogeneity across the included studies. There were significant differences in patient populations, in PSA regimens and coadministered drugs and in the measurement and reporting of outcomes. To overcome this limitation, we reported our results as qualitative summary narratives and captured general trends in each outcome measure. In spite of our inability to meta-analyse the information gathered, we believe our narrative represents the most complete review to date of remifentanil use in ED-like settings.

We found that remifentanil alone or in combination with other agents created agreeable PSA conditions. The notable exception to this finding occurred in one study that described severe anxiety in three paediatric patients.[22] In this study, children were premedicated with midazolam and then placed on an escalating remifentanil infusion. It is possible that the anxiolytic effect of midazolam wore off or was insufficient at the time of procedure performance. In almost all other paediatric studies, remifentanil was given concurrently with an anxiolytic or as a bolus immediately before the procedure. Since remifentanil produces only mild anxiolysis it may not be suitable as a sole agent for children requiring more than just pain control.[13]

There was no respiratory depression reported in any ED studies. Additionally, significantly increased respiratory depression did not occur in adult patients sedated using remifentanil. Conversely, it was frequently documented in children outside the ED. Most events responded to gentle stimulation, however, three studies reported children needing brief periods of PPV.[21 22 26] Interestingly, in all three of these studies, PPV was required in both remifentanil and control groups. When different dosing regimens were compared, higher doses of remifentanil were consistently associated with increased frequency and/or duration of apnoea or hypoxaemia.[20 21] When comparing per-kilogram dosing (with the exception of one ED study that reported no adverse events) children received higher doses of remifentanil than adults. Because remifentanil allows retained cognition even when respiration is depressed, adults may have been easier to coach through periods of would-be apnoea.[13] This may be difficult in uncooperative children making them intolerant to doses of remifentanil required for sedation. Overall, the data suggests that the risk of respiratory depression may be greater in paediatric but not in adult patients.

Although remifentanil did not increase rates of intubation, hospital admission or cardiac arrest, the frequency of such events is exceedingly rare[2] and none of the selected studies were powered sufficiently to detect them. Our results require

confirmation with trials specifically powered for important adverse events.

We did not identify any study evaluating resource utilisation. In an increasingly strained system, assessing the cost-benefit of remifentanil sedation is an important area for future research.

ED crowding is a universal problem and patient length of stay is now a reportable marker of quality assurance.[29] When comparing remifentanil to other agents, time to recovery and discharge was consistently shorter.[21 24–27] We found this to be the sole advantage of remifentanil use in the ED.

Overall, there is a paucity of existing knowledge on the use of remifentanil for PSA in the ED. Our review shows that remifentanil provides satisfactory PSA conditions for the performance of common ED procedures expedites recovery and discharge time when compared with other commonly used PSA agents. Nevertheless, we recommend that ED physicians exert caution when using remifentanil. Dosing was not standardised across any studies and therefore cannot be reproduced. Furthermore, respiratory depression was commonly reported in paediatric patients. The limitations of existing evidence emphasise the need for future high-quality research.

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Contributors MK and CV conceived the study. All authors reviewed the electronic search strategy. MK and HR reviewed articles. MK drafted the manuscript and all authors contributed substantially to its revision. MK takes responsibility for the paper as a whole.

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Provenance and peer review Not commissioned; externally peer reviewed.

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