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SUMMARY WITH CRITICAL APPRAISAL

Target-Controlled Infusion with Propofol and Remifentanil for Moderate Procedural Sedation in Medicine and Dentistry: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

BT	Bronchial thermoplasty
NRS	Non-randomized study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TCI	Target-controlled infusion
VAS	Visual analogue scale

Context and Policy Issues

Moderate sedation, also known as conscious sedation, is achieved by depressing the level of consciousness with drugs to reduce patient anxiety and discomfort and to improve examination procedure outcomes.[1] While under moderate sedation, patients are able to respond purposefully to verbal cues alone or in conjunction with light tactile stimulation.[2] Furthermore, cardiovascular function and spontaneous ventilation is typically maintained negating the need for patent airway management.[2] Thus, moderate sedation is used for various outpatient procedures such as endoscopy, colonoscopy, bronchoscopy, and dental procedures.[3]

The use of sedation medications may cause inadvertent over-sedation resulting in patients that are not easily aroused and/or require interventions to maintain patient airway.[3] Thus, clinicians performing moderate sedation should have the competence to manage adverse events related to unintentional over-sedation such as respiratory depression, blood pressure changes, and hypoxia.[2] Common medications used in moderate sedation may include propofol, short-acting opioids (e.g., remifentanil), and/or benzodiazepines (e.g., midazolam) administered intravenously by intermittent hand-bolus titration or target-controlled infusion (TCI) pumps.[4] The use of independent TCI pumps for the delivery of propofol and remifentanil allows trained operators to control and adjust the level of sedation during medical procedures.[5] Precise control of both agents is important as propofol has a narrow therapeutic range[6] and the addition of an opioid to propofol increases the risk of respiratory depression.[4] Equipped with a microprocessor, TCI pumps allow operators to specify the drug, pharmacokinetic model, patient characteristics (e.g., age and weight), and the effect-site concentration.[7]

The aim of this report is to summarize and critically appraise the relevant literature and evidence-based guidelines regarding the clinical effectiveness, cost-effectiveness and recommended use of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation in medicine and dentistry.

Research Questions

1. What is the clinical effectiveness of intravenous propofol and remifentanil administered by independent target-controlled infusion pumps for patients undergoing moderate procedural sedation in medicine and dentistry?
2. What is the cost-effectiveness of intravenous propofol and remifentanil administered by independent target-controlled infusion pumps for patients undergoing moderate procedural sedation in medicine and dentistry?
3. What are the evidence-based guidelines regarding the use of intravenous propofol and remifentanil administered by independent target-controlled infusion pumps for patients undergoing moderate procedural sedation in medicine and dentistry?

Key Findings

One non-randomized single-arm study was identified regarding the safety of intravenous propofol and remifentanil administered by independent target-controlled infusions pumps for patients undergoing moderate sedation for bronchoscopy. No relevant economic evaluations or evidence-based guidelines were identified regarding the cost-effectiveness or use of intravenous propofol and remifentanil administered by independent target-controlled infusion pumps for patients undergoing moderate procedural sedation in medicine and dentistry. Overall, the body of evidence was limited in quantity and quality.

Favourable visual analogue scale scores for dyspnea, pain, cough, and anxiety were reported by patients who received intravenous propofol and remifentanil administered by independent target-controlled infusion pumps operated by specialist sedation nurses. Additionally, favourable visual analogue scale scores for dyspnea, pain, cough, and discomfort were reported by bronchoscopists. Desaturation and hypotension occurred in four and two of 32 procedures, respectively, with no occurrence of serious adverse events.

The included study had several methodological limitations. The small sample size (N = 13) and lack of comparison to other sedation strategies should be considered when interpreting the findings of this report. Without comparator groups, it is unclear if these favourable safety outcomes are related to target-controlled infusions of propofol and remifentanil. Furthermore, statistical tests were not performed to evaluate changes from baseline for relevant outcomes.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were propofol and conscious sedation. For questions 1 and 2 no filters were applied to limit the retrieval by study type. For question 3 search filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and October 8, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (any age) undergoing endoscopy, colonoscopy, bronchoscopy, or dental procedures in hospital or community settings
Intervention	Moderate procedural sedation by intravenous propofol and remifentanil administered by independent TCI pumps

	Exclude: Anesthesiologist-administered TCI of propofol and remifentanil
Comparator	Q1,2: Moderate procedural sedation by intravenous propofol, short-acting benzodiazepine (e.g., midazolam, diazepam, lorazepam), and/or opioid analgesic (e.g., remifentanil, fentanyl, morphine, hydromorphone, meperidine) administered by intermittent hand-bolus titration; No comparator (safety outcomes only) Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., time to adequate sedation, sedation level achieved, time to recovery for discharge, patient satisfaction [e.g., health-related quality of life]); Safety (sedation-related adverse events, e.g., apnea, airway obstruction, desaturation, hemodynamics, disinhibition, allergy) Q2: Cost-effectiveness (e.g., quality-adjusted life year, incremental cost-effectiveness ratio, cost per patient adverse event avoided, cost per clinical outcome Q3: Recommendations regarding the use of intravenous propofol and remifentanil administered by independent target-controlled infusion pumps for patients undergoing procedural sedation in medicine and dentistry (e.g., optimal agents and doses, speed of titration)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

TCI = target-controlled infusion.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Guidelines with unclear methodology and those that did not contain relevant recommendations regarding the use of intravenous propofol and remifentanil administered by independent TCI pumps were also excluded.

Critical Appraisal of Individual Studies

The included publication was critically appraised by one reviewer using the Downs and Black checklist[8] for non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 429 citations were identified in the literature search. Following screening of titles and abstracts, 419 citations were excluded and 10 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 11 publications were excluded for various reasons, and one non-randomized study[9] (NRS) met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[10] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One primary NRS[9] was identified for inclusion in this review. Additional details regarding the characteristics of the included publication are provided in Appendix 2.

Study Design

The authors of the NRS conducted a prospective single-arm study.[9]

Country of Origin

The authors of the NRS were from the Netherlands.[9]

Patient Population

The included NRS involved 13 adult patients with severe asthma undergoing bronchial thermoplasty (BT). Since general anesthesia was needed for three of 35 BT procedures performed, 32 BT procedures were included in the analysis. The mean age was 42 years old and 85% participants were female.[9]

Interventions and Comparators

Participants undergoing BT in this single-arm study received remifentanil via TCI to a targeted plasma level of 1.5 µg/mL and propofol via TCI to a targeted plasma level of 1.2 µg/mL. The median total doses for propofol and remifentanil were 433 mg and 517 µg, respectively. The TCI pumps were operated by sedation anesthesiology nurses who had completed a one-year didactic and practical certification program. During the procedures, an anesthesiologist was on call as backup. The follow-up duration was not reported. All participants also received glycopyrrolate 0.2 mg, lidocaine 20 mg, midazolam 1 mg, and local anesthesia with lidocaine 1 mg/kg.[9]

Outcomes

The authors of the NRS evaluated primary outcomes including patient-rated degree of dyspnea, pain, cough, and anxiety and bronchoscopist-rated estimated degree of dyspnea, pain, cough, and discomfort for patient using visual analogue scales (VAS). Furthermore, sedation-related adverse events including desaturation, hypotension, or hypertension were also evaluated.[9] Full definitions regarding VAS scores are presented in Appendix 4.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Non-Randomized Study

The included NRS had strengths including clearly stated objectives, inclusion and exclusion criteria, intervention, outcome measures, and main findings.[9] Adverse events relating to moderate sedation were discussed. Estimates of random variability were reported and descriptive statistics were used to analyze the results. Finally, the authors disclosed that there were no conflicts of interest and reported their funding sources.

However, this NRS had methodological limitations such as lack of a sample size calculation and comparator groups evaluating other sedation strategies.[9] Since this study contained a small sample size (N = 13), the findings of this study may not be generalizable to patients in general. Furthermore, statistical tests were not used to assess for changes from baseline

for the main outcomes. Lastly, the generalizability of findings from this study to the Canadian setting was unclear since it was conducted in the Netherlands.

Summary of Findings

The overall findings of the identified study[9] that met the inclusion criteria for this report are highlighted below. Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of TCI-Delivered Intravenous Propofol and Remifentanil

Evidence regarding the safety of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation in medicine was available from one NRS.[9] Since this NRS was a single-arm study without a comparator group, clinical effectiveness outcomes were not summarized in this report. Full definitions regarding VAS scores are presented in Appendix 4.

As primary outcomes, median VAS scores rated by patients undergoing bronchoscopy procedures were favourable: 0.0 (dyspnea), 0.1 (pain), 0.5 (cough), and 0.1 (anxiety) (statistical analysis not conducted).[9] Additionally, median VAS scores rated by bronchoscopists performing the procedures were also favourable: 0.3 (dyspnea), 0.2 (pain), 1.2 (cough), and 0.6 (discomfort) (statistical analysis not conducted).[9]

Six adverse events and no serious adverse events (definition not provided) were reported.[9] Desaturation (i.e., oxygen saturation < 90% for > 30 seconds) occurred four times, with three cases restored with supportive care and one case converted to general anesthesia with tracheal intubation.[9] Two incidences of hypotension (i.e., > 20% decrease from baseline blood pressure) occurred, with both cases restored with intravenous ephedrine.[9]

Cost-Effectiveness

No relevant economic evaluations were identified regarding the cost-effectiveness of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation in medicine and dentistry; therefore, no summary can be provided.

Guidelines

No relevant evidence-based guidelines were identified regarding the use of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation in medicine and dentistry; therefore, no summary can be provided.

Limitations

Numerous limitations were identified in the critical appraisal (details in Appendix 3); however, additional limitations exist.

The evidence identified for this report was limited in quantity and quality. The lack of relevant randomized controlled studies and comparative NRS reporting on clinical effectiveness outcomes should be considered when interpreting the findings of this report. Furthermore, general anesthesia was required for three of the 35 BT procedures performed, so 32 BT procedures were included in the analysis.[9] Generalizability of the study findings was limited by several factors, including the small sample size (N = 13), patient composition, and setting. Since this included NRS[9] involved a higher number of

female participants (85%), the disproportionate female representation should be considered as women may report procedure satisfaction differently from men. As this study was conducted in the Netherlands, the findings may not be generalizable to the Canadian setting.[9]

No relevant economic evaluations or evidence-based guidelines were identified regarding the cost-effectiveness or use of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation in medicine and dentistry. Additionally, no relevant evidence was identified regarding the clinical effectiveness of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing endoscopy, colonoscopy, or dental procedures.

Conclusions and Implications for Decision or Policy Making

This review was comprised of one NRS[9] regarding the safety of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation during bronchoscopy. No studies reporting on clinical effectiveness outcomes with TCI pumps compared with alternative methods for providing procedural sedation were identified. No relevant economic evaluations or evidence-based guidelines were identified regarding the cost-effectiveness or use of intravenous propofol and remifentanil administered by independent TCI pumps for patients undergoing moderate procedural sedation in medicine and dentistry. Furthermore, no relevant evidence was identified for the clinical effectiveness or safety of intravenous propofol and remifentanil administered by independent TCI pumps for endoscopy, colonoscopy, or dental procedures.

Favourable visual analogue scale scores for dyspnea, pain, cough, and anxiety were reported by patients who received intravenous propofol and remifentanil administered by independent target-controlled infusion pumps operated by specialist sedation nurses (statistical analysis not conducted).[9] Furthermore, favourable visual analogue scale scores for dyspnea, pain, cough, and discomfort were reported by bronchoscopists (statistical analysis not conducted).[9] This study also reported clinical effectiveness outcomes like overall patient satisfaction and cooperation. These findings did not meet inclusion criteria for this report as there were no comparisons with alternative sedation methods; however, overall satisfaction levels as reported by patients and bronchoscopists were similarly favourable. While there were no serious adverse events, desaturation and hypotension occurred in four and two cases, respectively (statistical analysis not conducted).[9]

Overall, this identified primary study[9] had numerous methodological limitations which reduce confidence in the results. Specifically, without comparator groups evaluating other sedation strategies, it is unclear if the favourable safety outcomes can be attributed to TCI-delivery of propofol and remifentanil.[9] Furthermore, the small sample size (N = 13) calls into question the generalizability of this study's findings to patients in general.[9] Additionally, statistical tests were not conducted to assess for changes from baseline for relevant outcomes.[9]

Further research (i.e., large controlled clinical trials with comparator groups) investigating the clinical effectiveness and cost-effectiveness of TCI-delivered intravenous propofol and remifentanil, especially when administered by non-anesthesiologists and compared to intermittent hand-bolus titration, would provide additional knowledge base for clinicians performing moderate procedural sedation in settings without an anesthesiologist. Additionally, guidelines developed with rigorous methodology that are specific to the

Canadian context may help inform practice related to moderate procedural sedation using propofol and remifentanil delivered via independent TCI pumps.

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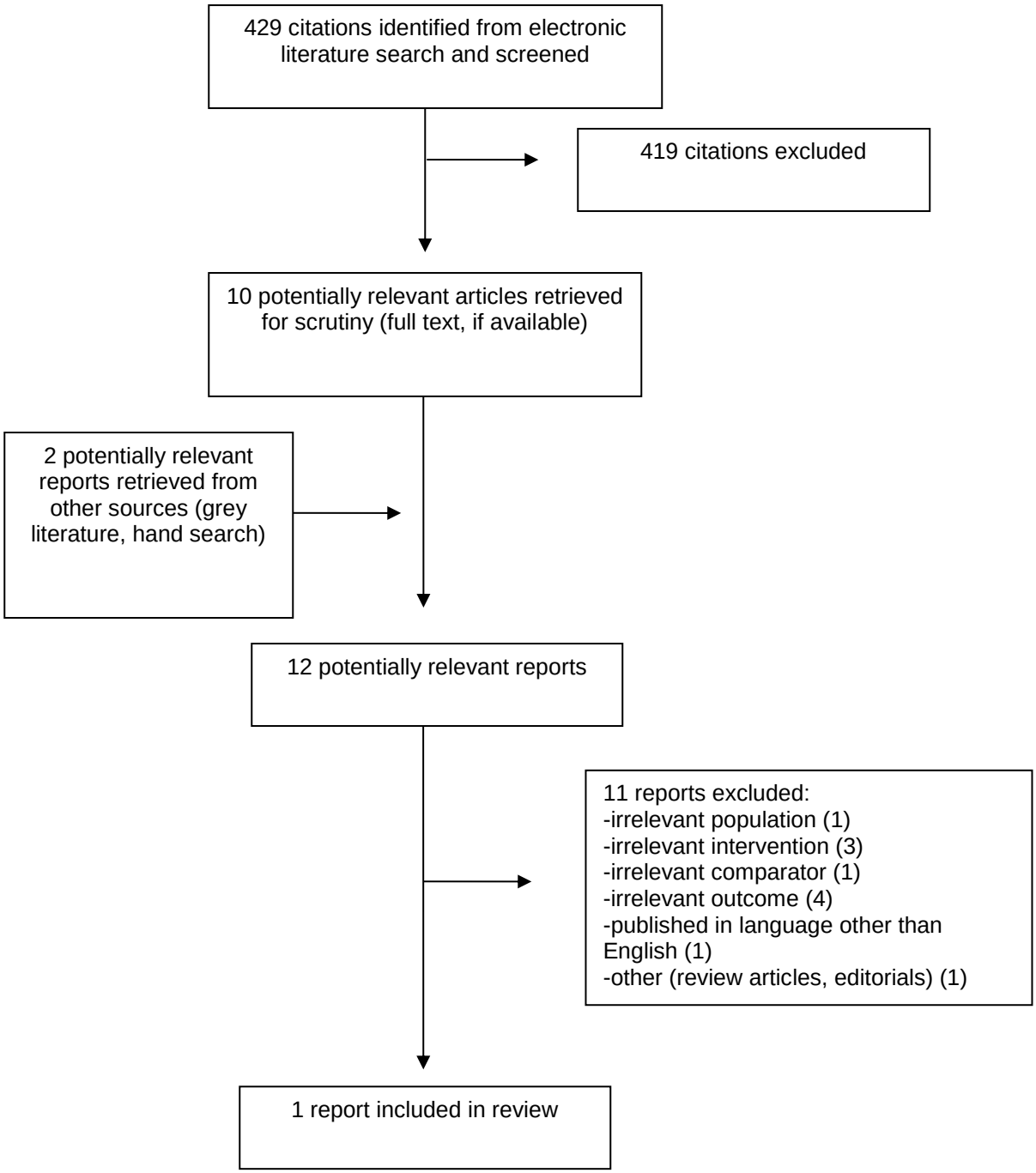
Appendix 1: Selection of Included Study



Appendix 2: Characteristics of Included Publication

Table 2: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
d'Hooghe et al. (2017)[9] The Netherlands Funding Sources: The Dutch Lung Foundation, The Netherlands Organization for Health Research and Development, and Boston Scientific	**Study design:** Prospective non-randomized study **Setting:** Department of Pulmonology at the Academic Medical Center hospital in Amsterdam **Objective:** To assess the safety, and patient and bronchoscopist satisfaction with propofol and remifentanil moderate sedation administered by target-controlled infusion (TCI) operated by sedation anesthesiology nurses	Adult patients with severe asthma undergoing bronchial thermoplasty (BT) **Number of patients:** N = 13 (32 BT procedures) **Mean age ± SD (years):** 42 ± 14 **% female:** 85%	**Intervention:** - Remifentanil TCI to a targeted plasma level of 1.5 µg/mL and propofol TCI to a targeted plasma level of 1.2 µg/mL **Comparator:** - No comparator Participants also received glycopyrrolate 0.2 mg, lidocaine 20 mg, midazolam 1 mg, and local anesthesia with lidocaine 1 mg/kg (to a maximum of 8.2 mg/kg)	**Relevant Outcomes:** - Primary outcomes: Patient-rated (i.e., degree of dyspnea, pain, cough, and anxiety) and bronchoscopist-rated (i.e., estimated degree of dyspnea, pain, cough, and discomfort for patient) using visual analogue scales - Sedation-related adverse events: desaturation (oxygen saturation < 90% for > 30 seconds), hypotension or hypertension (> 20% increase/decrease from baseline blood pressure requiring intervention) **Follow-up:** - NR

BT = bronchial thermoplasty; NR = not reported; SD = standard deviation; TCI = target-controlled infusion.

Appendix 3: Critical Appraisal of Included Publication

Table 3: Strengths and Limitations of Clinical Study Using the Downs and Black checklist[8]

Strengths	Limitations
d'Hooghe et al. (2017)[9]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section, and were valid and reliable • The inclusion and exclusion criteria were clearly described • Estimates of random variability were reported and descriptive statistics were used to analyze the results • Potential adverse events relating to the interventions were discussed • The authors disclosed that there were no conflicts of interest • Funding support for this study was reported	• This was not a randomized controlled trial, but a single-arm prospective study • Statistical tests were not used to assess for changes from baseline for the main outcomes • A sample size calculation was not conducted • The time period over which patients were recruited was not specified • Study was conducted in the Netherlands; findings may not be generalizable to the Canadian setting

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

Main study findings	Authors' conclusion
d'Hooghe et al. (2017)[9]	
Non-randomized prospective study of adult patients with severe asthma undergoing propofol and remifentanil moderate sedation administered by target-controlled infusion (TCI) for bronchial thermoplasty. **Primary Outcomes (median and interquartile ranges [IQR] in visual analogue scales [VAS[a]]):** • Patient-rated (n = 32) Dyspnea: 0.0 (0.0 – 0.6) Pain: 0.1 (0.0 – 1.0) Cough: 0.5 (0.0 – 2.1) Anxiety: 0.1 (0.0 – 0.7) • Bronchoscopist-rated (n = 32) Dyspnea: 0.3 (0.0 – 0.9) Pain: 0.2 (0.0 – 1.3) Cough: 1.2 (0.7 – 2.0) Discomfort: 0.6 (0.3 – 1.5) **Sedation-related Adverse Events (n = 32):** • Serious adverse events: 0 • Adverse events: 6 • Desaturation: 4 • Hypotension: 2 • Hypertension: 0 • Other: 0	"Moderate sedation with propofol and remifentanil TCI provided by specialized sedation anesthesiology nurses is feasible and safe and results in high satisfaction rates of both patients and bronchoscopists (p. 58)."[9]

BT = bronchial thermoplasty; IQR = interquartile range; SD = standard deviation; TCI = target-controlled infusion; VAS = visual analogue scale.

[a] = VAS scale 0 (no complaints at all) to 10 (enormously)

Appendix 5: Further Information

Previous CADTH Reports

1. Sedative agents during medical procedures: guidelines. (*CADTH Rapid response report: summary of abstracts*). Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/pdf/htis/2020/RB1462%20Procedural%20Sedation%20Guidelines%20Final.pdf. Accessed 2020 Nov 9.

2. Short-acting sedative agents during endoscopic retrograde cholangiopancreatography: a review of clinical effectiveness and guidelines. (*CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/rr/2020/RC1301%20ERCP%20Sedatives%20Final.pdf. Accessed 2020 Nov 9.

3. Propofol for conscious sedation during endoscopies: clinical effectiveness, cost-effectiveness, and guidelines. (*CADTH Rapid response report: summary of abstracts*). Ottawa (ON): CADTH; 2017: https://cadth.ca/sites/default/files/pdf/htis/2017/RB1157%20Sedatives%20for%20Endoscopy%20Final.pdf. Accessed 2020 Nov 9.

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Randomized Controlled Trials – Alternative Intervention

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Non-Randomized Study – Mixed Intervention

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Guidelines

No Relevant Recommendations

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