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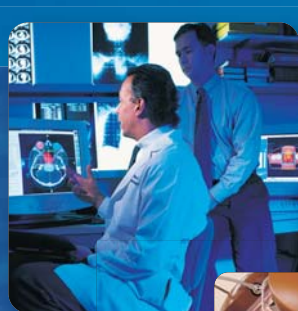
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Overview of Short-Acting Agents for
Procedural Sedation and Analgesia in
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Supporting Informed Decisions

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Canadian Agency for Drugs and Technologies in Health

**Overview of Short-Acting Agents for Procedural Sedation
and Analgesia in Canadian Emergency Departments**

May 2008

We thank Eugenia Palylyk-Colwell for her assistance in creating this overview from a longer report authored by Bond *et al.*

This overview is based on the Technology Report commissioned by CADTH: Bond K, Fassbender K, Karkhaneh M, Spooner C, Horton J, Sivilotti MLA, Campbell SG, Vandermeer B, Tjosvold L, Seal R, Rowe BH. *Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation* [Technology Report number 109]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.

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Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation

Technology

Short-acting agents for procedural sedation and analgesia (PSAs) propofol, ketamine HCl, etomidate, and ketamine combined with low-dose propofol (ketofol).

Condition

Adults who present to emergency departments (EDs) for painful procedures (i.e., treatment for bone fractures, major joint dislocations, cardioversion, and other procedures).

Issue

Short-acting agents have been perceived as superior to traditional agents, but uncertainty still remains regarding the optimal use of these agents, partly due to the lack of a comprehensive technology assessment in a Canadian context.

Methods and Results

A systematic review and survey of Canadian practice patterns was conducted. A systematic review of studies that compared short-acting procedural sedation drugs with one another or with conventional opioid and benzodiazepine agents for adult ED PSA was also conducted. Forty-four studies (nine randomized clinical trials, one prospective cohort, and 34 case series studies) were included: 32 evaluated propofol, 13 etomidate, 12 midazolam, eight ketamine, and two ketofol. A cost-minimization analysis was conducted. Propofol, etomidate, ketamine, and ketofol yield cost savings per procedure of \$335.70, \$301.76, \$244.41, and \$243.47 respectively, compared with standard therapy.

Implications for Decision Making

- **Clear differences exist between short-acting and traditional agents.** Short-acting agents are at least as effective as other regimens in terms of procedural success and clearly more effective in terms of reduced procedure time. With the exception of etomidate, short-acting agents were associated with no additional risk of minor adverse events (AEs) (and some may argue fewer risks of AEs).
- **Short-acting agents are associated with reduced costs.** Propofol, etomidate, ketamine, and ketofol yield cost savings per procedure of \$335.70, \$301.76, \$244.41, and \$243.47 respectively, compared with standard therapy. Etomidate generates the greatest savings from a time and labour costing perspective, but savings associated with propofol are greater because the differences in costs from hospitalization and AE rates more than offset the differences in labour costs.
- **Opportunities for optimal usage exist.** A survey of Canadian EDs revealed traditional agents are still in common usage. Opportunities may exist for the use of these agents by clinicians with less experience (e.g., rural physicians and nonphysician extenders, such as nurse practitioners and paramedics), given enough guidance or training.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Bond K, Fassbender K, Karkhaneh M, Spooner C, Horton J, Sivilotti MLA, Campbell SG, Vandermeer B, Tjosvold L, Seal R, Rowe BH. *Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation.*

1 Introduction

Canadians make more than 14 million visits to emergency departments (EDs) each year.¹ They often present with conditions that require the use of painful procedures. As a result, patients may be sedated using short-acting sedatives, analgesics (painkillers), or dissociative agents (drugs that inhibit the perception of sight and sound and produce feelings of detachment) that are given alone or in combination. This is called “procedural sedation and analgesia” (PSA), which is most often used in orthopedic manipulations (for example, bone fractures or major joint dislocations), cardioversion, abscess drainage, chest tube insertion, foreign body removal, and burn debridement.^{2,3}

The PSA process starts with the patient moving through triage, ED registration, preparation for the procedure, drug administration, and the procedure itself. The end of the process may be the end of the procedure, the end of sedation or awakening, the time when monitoring is no longer needed during recovery, or the point when the patient is admitted to hospital for further treatment or is discharged. As a result, the duration of the procedure can be viewed as variable. PSA practices also vary across North American EDs. This contributes to the uncertainty regarding PSA. Sites differ on approaches to patient selection, monitoring, personnel requirements, use of sedating agents, and criteria for safe discharge. Few sites routinely collect the data that are needed to show practice patterns and regional variations, so little is known about practice variations across Canada. What is known about Canadian practices shows that the location and acuity of the ED influence the type and proportion of PSA procedures.

Most of the old and new drugs that are used in PSA are administered intravenously. The drugs include propofol (Diprivan[®], AstraZeneca and generic manufacturers); ketamine (Ketalar[®], ERFA Canada and Ketamine Hydrochloride by Sandoz); etomidate (Amidate[®], Hospira Healthcare Corporation), which is available only through Health Canada’s Special Access Programme; and “ketofol,” which is ketamine combined with low-dose propofol. The unit costs range from C\$3.20 for 200 mg (20 mL) of propofol to C\$17.00 for 20 mg (10 mL) of etomidate. These drugs (except propofol, which lacks analgesic effect and is often combined with fentanyl for this reason) provide relaxation, analgesia, amnesia, and reduced anxiety. They have a rapid onset and short duration of action, properties that are ideal for use in busy EDs.⁴ Although there are limited data on standards of care in Canada, the available evidence suggests that small volume, single-physician coverage EDs generally use conventional opioids (fentanyl) or benzodiazepines (midazolam), whereas large volume, urban, multiple-physician coverage EDs use the newer dissociative agents alone or in combination with conventional agents (for example, ketamine and midazolam, propofol, and fentanyl).

Despite the perceived superiority of newer short-acting agents compared with conventional opioids and benzodiazepines for PSA, evidence on the relative use, efficacy, and safety of these short-acting agents for common painful procedures in Canadian EDs is limited. As a result, there is uncertainty about the cost-effectiveness of these agents compared with that of conventional agents and of each other. To develop clinical guidelines and effectively allocate resources, decision makers need to know if newer short-acting agents that are used in the ED are more effective and cost-effective than conventional agents and how effective and cost-effective these newer agents are relative to one another.

2 Objectives

Our objective was to conduct a systematic review and primary economic analysis for the evaluation of the clinical efficacy, safety, and cost-effectiveness of short-acting and dissociative agents for PSA in adults who present to EDs for painful procedures. To achieve these objectives, the following research questions were addressed:

- How are these brief painful procedures managed for adult patients who present to Canadian EDs?
- What techniques and pharmacological agents are used for adult patients who present to Canadian EDs?
- What is the comparative efficacy (in terms of procedural success, procedure time, pain, recall, and satisfaction) and safety of short-acting and dissociative agents when compared with each other and with opioid and benzodiazepine agents for adults who present to the ED and who require brief painful procedures?
- What are the barriers to the use of short-acting and dissociative agents for adult patients who present to EDs and who require brief painful procedures?
- What is the cost-effectiveness of using short-acting and dissociative agents compared with opioid agents used alone or in combination with benzodiazepine agents in adults who present to the ED and who qualify for procedural sedation?

3 Survey

A survey of Canadian and Alberta practice patterns was conducted. A comprehensive survey of Alberta EDs showed that urban EDs use PSA more often for cardioversion and other painful procedures than do rural sites, yet both treat fractures and dislocations in similar ways. Urban EDs tend to use propofol as the primary agent, whereas rural EDs use opioids and benzodiazepines. Staffing differences between the two, and thus the ability to follow staffing guidelines for PSA use, may explain the variations, which likely exist in other Canadian provinces.

4 Clinical Review

Methods

Published clinical literature was obtained by searching the Academic Search Premier, BIOSIS Previews, CINAHL, Cochrane Anaesthesia Review Group register, Cochrane Central Register of Controlled Trials, Dissertation Abstracts, EMBASE, Health Source: Nursing/Academic Edition, International Pharmaceutical Abstracts, MEDLINE, OCLC Papers First, Pascal, Scopus, and Web of Science databases using pre-defined search terms with no language restrictions. Details of the search strategy appear elsewhere.⁵ Grey literature was obtained by searching the reference lists of included studies, abstracts in medical journals, government and professional association documents, theses and dissertations, and the Internet. Original searches were performed in May 2007 and updated in selected databases in November 2007. Pharmaceutical manufacturers were

contacted for information about unpublished completed or ongoing studies of propofol, prevalence of the use of these agents for PSA in Canada, and the agents' cost-effectiveness.

After the studies were screened, two reviewers independently selected potentially eligible studies where the publication type was a primary research report (experimental or observational studies); the design was a clinical trial, controlled before-and-after study, or prospective observational study (for example, cohort, interrupted time series, case series); the population was more than 50% adult patients who required brief, painful procedures; the setting was a hospital ED; the intervention was etomidate, ketamine, propofol, or combination ketofol; the comparator was an opioid in combination with a sedative-hypnotic benzodiazepine or regional anesthesia; and the outcome was numeric data on at least one outcome of interest (procedural success or time, pain, recall, satisfaction). Studies on elective ED procedures were excluded.

A reviewer independently extracted data from each included study using a pre-tested, structured form. Results were verified by a second reviewer before data entry into a spreadsheet. Extracted data included study design; population characteristics; and PSA practice pattern including drug used, dosage, time of procedure, setting, indications, procedural efficacy, and adverse events (AEs). Evidence tables were used to summarize the study characteristics. Study quality was independently evaluated by two reviewers using the Jadad scale⁶ and the Schulz criteria for allocation concealment⁷ for randomized controlled trials (RCTs), the Newcastle-Ottawa Scale (NOS)⁸ for prospective observational studies, and a 15-item tool developed by the reviewers to assess bias for case-series studies.⁵

Whenever possible, efficacy data were analyzed by pooling data. Risk ratios or odds ratios and corresponding 95% confidence intervals (CI) were used to summarize dichotomous outcomes. Weighted mean differences and standardized mean differences with 95% CI were used for summarizing continuous outcomes. Random effects models were used in all instances, and study heterogeneity was estimated using the I^2 statistic.⁹ Information on subgroup analyses, assessment of publication bias, mixed treatment analyses, and statistical methods appears in the Technology Report.⁵ When pooling safety data, studies that did not report data for an AE were excluded (no assumption was made that if it was not reported, the event did not occur). Studies that reported no clinically significant AEs were also excluded from the pooled risk estimate. If studies reported more procedures than patients (some patients required additional PSA at a later date), the probability of AEs was calculated by dividing the total number of major AEs by the total number of patients exposed to the drug. Any reviewer differences in study selection, data extraction, or quality assessment were resolved by consensus or adjudication by a third reviewer.

Results

From 1,794 citations that were identified from the original searches, 1,546 were excluded, resulting in 248 potentially relevant studies. Eight studies from the grey literature and 12 studies from the search update were added for a total of 268 studies. A further 200 studies were excluded to yield 68 studies that were considered to be relevant in addressing the four research questions. Of the 68 studies, 47 were included in the clinical review (including three multiple publications), resulting in 44 unique studies (reporting on 12,404 PSA episodes) that met the selection criteria. Details about the included studies (study characteristics and quality assessments) appear in the Technology Report.⁵

Of the 44 studies, nine were RCTs,¹⁰⁻¹⁸ one was a prospective cohort study,¹⁹ and 34 were case series with no controls. Most studies took place in the US. The number of participants ranged from 11 to 4,500 (median of 74.5), and the age of participants ranged from one month to 92 years. Orthopedic reductions of fractures or joint dislocations were the most frequent procedures performed, followed by abscess drainage, laceration repair, and cardioversion. Propofol was the most common PSA drug used as an intervention or control (32 studies), followed by fentanyl (15 studies), etomidate (13 studies), midazolam (12 studies), ketamine (eight studies), morphine (seven studies), ketofol (three studies), and methohexitol (two studies). More than one drug could have been evaluated in a study. The RCTs were of moderate quality (median Jadad score of 3, range 2 to 4), as were the case series (80% of studies fulfilled at least half of the quality criteria). The cohort study was considered to be of good quality (7/12 on the NOS).

a) Efficacy

There were few direct RCT comparisons of short-acting agents for PSA, and no more than three studies could be combined to provide an efficacy estimate for any of the reported outcomes. Most studies involved a newer PSA agent(s) compared with midazolam with or without a parenteral analgesic. The available evidence suggests that etomidate, ketofol, and propofol are at least as effective as other regimens in terms of procedural success and more effective in terms of reduced procedure time. Pooled estimates of pain ratings, patient recall, and patient or physician satisfaction could not be calculated, because of the use of incomparable measures and drug comparisons for these outcomes. Estimates from individual studies suggest that the differences between drugs for these measures are negligible and often not statistically significant.

b) Harms

The combination of observational and RCT evidence showed that the newer agents (except etomidate) have AE rates at least as low and often lower than those of conventional agents (commonly midazolam with or without fentanyl). Propofol had the lowest probability of total AEs, followed by ketamine, ketofol, conventional agents, and etomidate. Ketamine and ketofol had the lowest rates of hypotension, followed by conventional agents, propofol, and etomidate. Because of the sensitivity of monitoring in RCTs, higher AE rates in the RCTs than those reported in larger observational studies were found for all agents. All AEs except one were transient, easily managed, and had no long-term sequelae.

5 Economic Review

Methods

Published economic literature was obtained by searching the Academic Search Premier, BIOSIS Previews, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Dissertation Abstracts, EMBASE, Health Source: Nursing/Academic Edition, Health Technology Assessment Database, International Pharmaceutical Abstracts, MEDLINE, NHS Economic Evaluation Database, Ref-PRO, and Web of Science databases using pre-defined search terms with no language restrictions. Details of the search strategy appear elsewhere.⁵ Additional hand searches of reviews and guidelines, abstracts published in certain medical journals, theses and dissertations,

unpublished studies, and studies in progress were conducted. Reference tracking and a Science Citation Index forward search were also used to identify relevant studies.

After the studies were screened, two reviewers independently selected potentially eligible studies by using selection criteria that were similar to those in the clinical review, except that the outcomes were event probability, resource use, or costs. Any reviewer differences in study selection were resolved by consensus or adjudication by a third reviewer. A reviewer independently extracted data from each included study using a data abstraction form and entered the data onto a spreadsheet. Results were cross-checked for accuracy and completeness by a second reviewer. Extracted data included study design, population characteristics, treatment outcomes (success, procedure time, AE rates, and their definitions) and resource use and costs (for example, complication rates, manipulation times, recovery times, and staffing and drug costs).

Results

The electronic search resulted in 2,501 citations. From these, 2,300 were excluded, leaving 201 potentially relevant studies that were retrieved for further scrutiny. From these, 175 were excluded, to yield 26 included studies. Fifteen studies were added from the grey literature search. This resulted in 41 included studies, including four economic evaluations^{10,15,20,21} and 37 studies that provided costing and probability data. The characteristics of all included studies appear in the Technology Report.⁵

There were 17 efficacy analyses, 14 outcome descriptions of one agent, four economic evaluations, three cost-outcome descriptions for one agent, two cost-analyses, and one cost description of a single agent. Of the four economic evaluations, one¹⁵ examined the use of short-acting agents. Most studies were reviewed to provide insight into the resource use profile of PSA. The variation in the methods used prevented the reporting of average actual resource use. Nonetheless, synthesis of the studies allowed us to construct a comprehensive model of resource use that included appropriate personnel in the ED, identification of costs associated with complications, lack of procedural success, and hospitalization, to which standard costing methods were applied in our economic analysis.

6 Economic Evaluation

Methods

A cost-minimization analysis was conducted to compare propofol, ketamine, etomidate (or the drugs used in combination; for example, ketofol), and conventional analgesic and amnestic agents for adult patients with fractures, dislocations, or non-elective cardioversion who receive PSA in EDs. The primary variable that we examined was procedure cost. Effectiveness that was based on rates of admission to or readmission to hospital or higher overall use of health care resources was also examined for the subgroups. Health service events that were captured included direct medical costs in the ED and those after discharge from the ED (for example, hospitalization, physician visits, subsequent admissions to EDs, and outpatient medications) for a maximum of eight weeks. Events beyond eight weeks could not be attributed to the initial PSA.

Resource use that was associated with the health service events was based on actual practices. Information on event probabilities, resource use, and costs was drawn from the economic and clinical literature, a national survey of EDs, data collected from specific Canadian sites, a time-in-motion study, Canadian health authorities (for example, Capital Health), unpublished studies and reports, and expert opinion. A time-in-motion study was conducted at the University of Alberta Hospital ED as part of this project to collect more data about the time spent on and costs associated with PSA for the treatment of fractures, dislocations, and cardioversion. A costing model was developed to combine all the resources that were used from the time of admission to the ED until discharge and that were attributed to each sedation strategy (to account for differences in sedative agents, personnel, procedural success, AEs, and hospitalization). Resource uses that did not vary by sedation strategy (for example, capital and overhead) were omitted from our analysis. The costing perspective was that of the Ministry of Health. Costs, probabilities, and outcomes were combined to estimate the cost differences between sedation strategies. The decision analytical model appears in the Technology Report.⁵

In the base case, the valuation of resources is reported for Alberta in 2007 Canadian dollars. The modelling assumptions pertaining to the sedating agents, personnel, hospitalization, AEs, treatment time, ED staffing, and probability of procedural success, AEs, and hospitalization are described in the Technology Report.⁵ The costs that were associated with individual events were calculated by multiplying the unit costs (based on the Alberta market) by the quantity of resources consumed. In the decision analytic model, expected costs were obtained by multiplying “Canadian” quantities by “Alberta” prices. Variations in practice are based on observed differences in quantities used by individuals. These were greater in magnitude than the variations in prices between provinces. In the base case, an expected cost was obtained for each of the five drug strategies and for the three conditions. As in a cost-minimization analysis, the costs of standard therapy were subtracted from the costs of each of the newer sedation strategies. One-way and multi-way sensitivity analyses were conducted to test the underlying assumptions in the model.

Results

In the base case, the expected cost per procedure (attributed to the drug, labour, hospitalization, and AEs) was C\$138.76 (propofol), C\$172.70 (etomidate), C\$230.05 (ketamine), C\$230.99 (ketofol), and C\$474.46 (standard therapy). As a result, propofol yielded the greatest cost savings (C\$335.70) per procedure compared with standard therapy, followed by etomidate (C\$301.76), ketamine (C\$244.41), and ketofol (C\$243.47). Although propofol generates the greatest overall savings because of its low hospitalization and AE rates, etomidate generates the greatest savings from a time and labour costing perspective. Nonetheless, the savings with propofol remain greater because differences in costs associated with hospitalization and AE rates more than offset the differences in labour costs. Sensitivity analyses were used to examine the uncertainties due to the costs of drug and labour and hospitalization rates. Assuming a 50% discount on drug prices, propofol continued to dominate. Propofol also yielded the greatest savings estimate over a range of high and low labour costs. When high and low costs from hospitalization and AEs were combined, propofol again emerged as the dominant strategy in all cases.

7 Limitations

As with all systematic reviews, our results are limited by the available evidence. There was an insufficient number of trials to assess the potential for publication bias in the reporting of efficacy outcomes. Nonetheless, steps were taken (for example, a comprehensive search strategy including hand-searching of conference proceedings to identify unpublished studies) to minimize this bias. We are aware of many North American centres where PSA use with these agents is routine, yet publication of the safety and efficacy data has not been forthcoming. Selection bias is always possible, but all abstracts and primary manuscripts were screened by two independent reviewers using standard eligibility criteria. Few comparative trials were found among the included studies, so the evidence on which our conclusions are based is sparse. The use of RCTs and observational studies for the AE data may have biased the results, and the reporting of data in aggregate precluded the evaluation of AEs for short-acting agents used alone versus in combination with conventional agents. There was also variability in the actual dosage of drugs and supplemental drugs that were used in the studies. This may result in a bias in drug costs if standard dosages are assumed. Compounding this is the fact that PSA drug prices were not observable, and waste could not be quantified. The potential for bias is limited because the savings due to drug costs were comparatively small.

Cost differences for the PSA drugs were calculated using the combined procedure times for each drug as reported in individual studies and the “not reported” differences between times for drugs. As a result, the combined time estimates vary based on the procedures included in the studies. There is uncertainty in the comparison of labour costs between agents. In our base case, we used the staffing levels (for example, two physicians, a nurse, a respiratory therapist with or without an orthopedic technician, depending on the condition) in busy, tertiary care EDs where typically many PSA procedures are conducted each year. In centres where PSA is less common, the patient acuity is less severe, and where staff shortages exist, staffing levels may be lower. This may influence the magnitude of the results. They would, however, apply to all estimates and should not change the overall results.

8 Health System Implications

Assuming that PSA is being performed between seven and 13 times out of every 1,000 ED visits as shown in our survey of Canadian practice patterns,⁵ and considering the base-case model where propofol is the preferred agent, the Canadian health care system could realize savings between C\$33.8 million and C\$59.7 million (C\$335.78 per case) compared with standard care. Because many large urban EDs report using short-acting PSA agents, these values represent an upper estimate. The incremental savings of switching to propofol will be lower if ketamine, etomidate, or ketofol are being used. These results suggest that cost savings are likely to vary by location so that the actual cost savings may be lower than these estimates.

9 Conclusions

This report strengthens the view of emergency medicine researchers that short-acting sedatives induce deep sedation easily and reliably and to a degree that is unattainable when midazolam and fentanyl are used. Moreover, they do so with associated AEs that are almost entirely predictable, not serious, and transient and that respond to simple measures in the ED. While agents can be used alone or in combination (for example, ketofol) for PSA, no efficacy superiority emerged. Etomidate seems to produce the most AEs, and there is evidence that AEs may be less pronounced with the combination of ketamine and propofol. Evidence remains sparse, however, and the position of this combination of agents in PSA remains unclear. Given that emergency physicians have the qualifications for administering deep sedation and dealing with the generally transient complications, PSA seems to be safe when administered by these individuals. Low event rates and the incomplete reporting of AEs prevent us from commenting about the rare complications associated with PSA agents.

Previous health economic evaluations of PSA have been limited in number and scope. This economic evaluation used data from several sources (for example, clinical reviews, surveys, and expert opinion) to reflect actual practice in Canadian EDs. Overall, the results suggest that propofol is the dominant strategy compared with other short-acting agents, and this dominance occurs under various scenarios and assumptions. We suggest that this conclusion is unlikely to vary across Canadian EDs.

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