Examining the incidence of DELIRIUM in Canadian Cardiac Surgery patients: a protocol for the DELIRIUM-CS Canada cross-sectional study.

The DELIRIUM-CS Investigators* on behalf of The Canadian Cardiovascular Critical Care (CANCARE) Society Investigator Group and the Canadian Critical Care Trials Group

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Abstract

Background: As a recognized complication of cardiac surgery, increasing attention has been paid to the negative effect of delirium on post-operative outcomes. Despite this, little is still known about the true incidence of delirium following cardiac surgery, with published rates ranging widely from 3% - 78%. This study aims to use validated and easily implementable bedside tools to determine the incidence of delirium in a contemporary cardiac surgery population.

Methods: The DELIRIUM-CS Canada study is a multicenter cross-sectional cohort study. Over a three month period, all patients undergoing major cardiac surgical procedures at each of the participating centers will be screened for post-operative delirium using either the Intensive Care Delirium Screening Checklist or Confusion Assessment Method for the Intensive Care Unit tool. Delirium screening will be conducted for either up to 7 days following their date of surgery or up until their date of initial discharge from the intensive care unit, whichever comes first. In addition to reporting an overall rate of delirium, unadjusted and adjusted incidence rates of delirium will be reported by institution and for the entire cohort. Risk-adjustment will be performed using multivariate regression modeling techniques.

Interpretation: The results of this study will provide valuable insight into the true burden of delirium among patients having undergone a major cardiac surgical procedure in the current era. This is the first step in creating a multifaceted delirium prevention/treatment clinical pathway for the cardiac surgery patient.

Trial Registration: ClinicalTrials.gov register Number: NCT02206880

Keywords: delirium; cardiac surgery; prevention; screening tool; confusion assessment method

Introduction

Delirium is an acute confusional state characterized by fluctuating mental status, inattention, and either disorganized thinking or altered level of consciousness.[1–5] It has long been recognized as a complication of cardiac surgery, a condition more likely to be experienced among older adult patients and those with greater comorbid disease burden.[6–8] In recent years, increasing attention has been paid to the negative effect of delirium on health care costs and post-operative outcomes, including long-term survival, freedom from hospital readmission and reduced cognitive and functional recovery.[9-18] Despite this, little is known about the true burden of delirium among patients having undergone a cardiac surgical procedure. Reported rates of delirium range widely, with rates as low as 3% but as high as 78% depending on the type of cardiac surgery, the method of detection, and the definition of delirium being used.[7,9–14] Despite its strong association with adverse post-operative events, delirium is an often under-recognized source of end-organ dysfunction. In the absence of an active screening program, delirium can go undiagnosed in greater than 70% of cases.[15,16]

Over the past two decades, the risk profile of patients undergoing cardiac surgery has changed. Increasingly, cardiac surgical procedures are being performed on older patients with recent coronary syndromes, higher New York Heart Association classifications, lower left ventricular ejection fractions and cardiogenic shock, all of which are associated with increased rates of postoperative delirium.[6,14] While the precise incidence of delirium in the current era of cardiac surgery is unclear, it is likely that it will continue to increase due to the aging demographic of the "typical" cardiac surgery patient. Therefore, quantifying the magnitude of delirium in a large contemporary sample of the population is the first critical step in addressing the prevention and treatment of this important, common and yet life-threatening complication.

The CANadian CARdiovascular critical carE (CANCARE) Society (www.cancaresociety.com), founded in 2009, is a multidisciplinary group created to improve the quality of care of critically ill cardiovascular patients using multidisciplinary expertise in a cooperative model. The founding committee has identified postoperative delirium (PoD) in the cardiac patient as a national priority for investigation and initiated planning of the DELIRIUM-CS Canada Study in the summer of 2011. Through a network created within the CANCARE society, the aims of this study are threefold: (1) To identify the true burden of delirium using a "standardized" definition among patients having undergone a cardiac surgical procedure in 11 centers across Canada; (2) To determine the impact on healthcare utilization (as determined by intensive care unit (ICU) and hospital length of stay (LOS)) and postoperative mortality; and (3) To determine modifiable and non-modifiable risk factors for the occurrence of delirium in a large, multicentre cohort of contemporary cardiac surgery patients. We hypothesize that delirium, identified through a systematic and standardized postoperative screening protocol is a highly prevalent, though variable, condition following cardiac surgery. Secondly, we hypothesize that the occurrence of PoD is associated with prolonged hospital LOS and other negative outcomes.

Methods and Analysis

The DELIRIUM-CS Canada study is a multicentre cross-sectional cohort study designed to determine the incidence of delirium across 11 cardiac surgery centers in Canada using a standardized delirium screening methodology. The trial has been registered on National Institutes of Health ClinicalTrials. gov (NCT02206880). This study has been approved by the University of Manitoba Research Ethics Board (REB) as well as the REB at each of the participating centers. The study will be conducted in accordance with the International Conference on Harmonisation and Good Clinical Practice principles.

Setting

The DELIRIUM-CS study will be conducted in 11 centers across Canada: Edmonton, AB; Calgary AB; Winnipeg MB; Hamilton ON, Newmarket ON, Toronto ON, Ottawa ON, Montreal (two sites) QC, Saint John NB and Halifax NS. Over a three-month period, all patients undergoing cardiac surgical procedures at each of the participating centers will be screened for post-operative delirium.

Each site will have identified personnel for the collection and entry of data for the study.

The Site Principal Investigator (PI) will be responsible for the conduct of the study and ethics approval at that site. Site communications and study documents will be sent to hospital PIs in addition to any nominated research personnel associated with that site.

Participant Selection

Inclusion Criteria

All patients undergoing cardiac surgery who are admitted to an ICU or cardiac surgery recovery unit (CSRU) following their procedure. Patients will not be excluded on the basis of urgency or procedure type.

Exclusion Criteria

Patients in whom delirium cannot be reliably tested(e.g., previous debilitating stroke, cerebral palsy, previous history dementia, recent history of a psychotic disorder, severe hearing disabilities or inability to understand English or French, active seizure disorder or Child-Pugh class B or C cirrhosis) or with known preoperative delirium. Cardiac surgery procedures that do not require an admission to an ICU (i.e. pacemaker insertion or sternal debridement admitted to the ward) will be excluded.

Screening Tools

Each centre will be allowed to employ either the Intensive Care Delirium Screen Checklist (ICDSC)[1] or the Confusion Assessment Method – Intensive Care Unit (CAM-ICU)[3] tool (Table 1) to detect delirium. Similarly, either the Riker Sedation Agitation Scale (SAS)[27] or the Richmond Agitation-Sedation Scale (RASS)[28] will be used to determine levels of sedation and agitation (Table 2). A Sedation/Agitation score will need to be paired with each delirium screening assessment. It is up to the centre to decide which tool they wish to use. The Richmond Agitation-Sedation Scale and Sedation-Agitation Scale are the most valid and reliable sedation assessment tools for measuring quality and depth of sedation in adult ICU patients.[29] Simultaneous sedation assessments are important to differentiate delirium assessments confounded by sedation level with delirium independent of concomitant sedation[30].

A delirium screen with either the ICDSC or CAM-ICU should be performed at least every 12 hours (i.e. once per shift, with the first assessment in the morning and a second assessment with the beginning of the evening shift) and should be performed concomitantly with either the SAS or RASS assessment.

Data Sources and Collection

Data will be extracted prospectively from patient clinical records at each participating site for the purposes of completing their respective cardiac surgery database/registry. Delirium screening will be conducted by trained bedside personnel on all patients admitted post-operatively to the ICU or CSRU, starting on the first postoperative day. Delirium screening will be conducted for 7 days following their date of surgery (i.e. postoperative day #1) or until their date of initial discharge from the intensive care unit, whichever comes first. Data relating to the delirium and sedation scales will be captured in the accompanying CRF.

In addition to administering the delirium and sedation/agitation screening tools, data regarding baseline demographic and clinical characteristics as well as data regarding the procedure performed (see Case Report Form (CRF)). Baseline data collected for each patient will include*:* date of surgery,

surgical procedure, procedure urgency, sex, age, ICU admission date and time, co-morbidities (hypertension, diabetes, hyperlipidemia, smoking history, chronic obstructive pulmonary disease, peripheral vascular disease, previous cerebrovascular accident), EUROScore II, and length of stay in both ICU and hospital. Delirium episode data will include each of the CAM-ICU/ICDSC and RASS/SAS scores, the attending physician's diagnosis of delirium, and whether or not the patient is receiving pharmacologic therapy for delirium episode. As this is a cross-sectional study using data collected as part of routine clinical practice, no safety monitoring will be undertaken.

Statistical Analysis

Measured Outcome

Patients will be considered as having had post-operative delirium if the results of at least one of the screening tests administered yielded a positive finding of delirium more than 6 hours after anesthesia emergence (defined as stopping sedation in either the operating room or in the postoperative intensive care unit). In addition to reporting an overall rate of delirium, unadjusted and adjusted incidence rates of delirium will be reported by institution. Crude rates for delirium will be reported with the potential of generating a risk model using multivariate regression modeling techniques to determine predictors of PoD in patients following cardiac surgery.

Sample Size

As the primary goal of this study is to determine the incidence of postoperative delirium, there is no required sample size that has been calculated for this study. However, based on our[19] and other recent analyses[13,17,18], the average surgical volumes of each of the centers involved, we expect approximately 150-400 patients per site to be enrolled for the three month evaluation period.

Data Management

The data management and analysis will be undertaken by the St. Boniface Hospital/I.H. Asper Clinical Research Institute. The principal means of data collection and data processing will be via electronic data entry at each site. Data will be exported to the St. Boniface Hospital/I.H. Asper Clinical Research Institute stripped of any patient identifiers. Each patient will be given a site and an anonymous unique study number. No site monitoring will be performed. De-identified data will be entered by each participating site into an electronic CRF. Master log sheets with identifying details will remain confidential and will be stored securely at participating sites to enable data queries to be addressed if required. Master log sheets or any other identifying information will not be submitted to the study office at the St. Boniface Hospital. All data collected by the study will be kept for a minimum of 7 years, or as otherwise required by regulatory authorities. The St. Boniface Hospital/I.H. Asper Clinical Research Institute will be the data custodians and all electronic data will be stored and backed up on password-protected servers. All paper data will be archived and stored in a secure facility at each participating centre. Data entered by each site will be password-protected and the ability to access or change data prior to locking of the database will be restricted to that site and staff managing data at the St. Boniface Hospital. Once initial data collection has been completed, missing data and implausible values will be identified using predetermined objective criteria, and queries resolved through direct communication with sites if required. This data cleaning process will be overseen by the DELIRIUM-CS Canada management committee.

Trial Monitoring and Oversight

The DELIRIUM-CS Canada management committee is responsible for all aspects of study design, management, analysis and publication of results. In addition, the management committee is responsible for ensuring that the study meets the proposed milestones and deadlines.

Regulatory Requirements

This study is low-risk and will not affect patient management in any way. Delirium screening is considered an accreditation standard in Canadian ICUs and routinely performed as part of daily assessments.[31] Finally, given that data will be collected at participating sites from de-identified medical records, procedures will be put in place to protect patient privacy. Information identifying individual patients will be kept confidential at each site and will be stored securely. This will allow data queries to be addressed, which is essential to ensure data integrity, but this information will not be sent to the St. Boniface Hospital/I.H. Asper Clinical Research Institute. De-identified data sent to the St. Boniface Hospital/I.H. Asper Clinical Research Institute will be stored securely in locked files or password-protected electronic files. Data from individual patients will be combined and will not be presented in a manner that would allow the identification of any individual patient.

Participating ICUs are involved voluntarily, and there is implied consent from participating units, indicated by their agreement to participate and a memorandum of understanding if necessary will be signed between the participating ICUs and the St. Boniface Hospital/I.H. Asper Clinical Research Institute.

Interpretation

Herein we described our multicenter cross-sectional study, which aims to determine the incidence of delirium across 11 cardiac surgery centers in Canada using a standardized delirium screening methodology. This study will be the first to report on incidence rates of new delirium following cardiac surgery across multiple centers employing standardized screening methodologies. The advantages of this employed approach is that data from high volumes centre, both academic and community site will be collecting all consecutive patients in the same time period. Therefore, quantifying the magnitude of delirium in a large contemporary sample of the population is the first critical step in addressing the prevention and treatment of this important, common and yet life-threatening complication. Secondly, the study will provide a pragmatic rates delirium detection using bedside personnel. The advantage of this approach is that it will provide valuable insight into the "real-world" detectable burden of delirium among patients having undergone a cardiac surgical procedure in the current era. While it would be ideal to have reference standard of a trained research personnel or other reference standard, it would not have been possible for this study. This may therefore result in under-reporting of the actual delirium rates. Nonetheless, each site will have undergone extensive training of bedside personnel using implementation strategies that have been shown to be effective in delirium detection.[19–26] Ultimately it is anticipated that this initiative will be an important first step in creating a multifaceted delirium prevention/treatment clinical pathway for the cardiac surgery patient.

Limitations

Given the observational nature of the study, efforts have been made to address potential sources of bias in our study. To mitigate the effects of participant selection bias in our study, patients will not be excluded on the basis of urgency or procedure type. At the institution-level, we will compare incidence rates of post-operative delirium between both academic and non-academic participating sites. A

potential limitation that must be considered how a handle data generated from a centre(s) with a low screening rate (and perhaps too high). Upon completion of data collection for all reporting centres, we will need to consider a threshold below which the centre's data will not be included.This may provide the opportunity to make novel contribution in that we may able to “test” approaches to implementation of screening tools in each institution. Indeed, it may be that some centres may be better or have improvements over the 3 months of collection. We will consider the use of a sensitivity analysis to examine how predictors change with the inclusion and exclusion of certain sites with either high or low screening rates. The variability in the reporting, in of itself, may be quite revealing. This may offer opportunity to look at barriers to implementation on a more qualitative manner and open the door to mixed methods analysis. Although screening for delirium is an accreditation standard in Canadian ICUs, compliance rates with the use of the screening tools will be assessed, and potential barriers to implementation of the tools identified.

Knowledge Translation

We will use the “Strengthening the Reporting of Observational Studies in Epidemiology” (STROBE) Statement that are guidelines for reporting observational studies.[26.] Data collected in the study will be presented at the Annual Scientific Meeting of the CANCARE Society Investigator Group, Scientific Meetings of the Canadian Critical Care Trials Group, and other forums as deemed appropriate. Data will subsequently be used for scientific publications in academic journals.

Conclusions

In summary, we describe the protocol for the DELIRIUM-CS Canada study. Our study proposes to determine the true incidence of delirium among Canadian cardiac surgery patients using a standardized delirium screening methodology, as a first step in creating a national prevention/treatment clinical pathway for the cardiac surgery patient.

Competing Interests

The authors declare that they have no competing interests.

Contributors

This study will be published under the authorship of the CANCARE Society Investigator Group investigators with the writing committee listed as primary authors. All participating investigators will be listed under such group identifier in an appendix.

Funding

The study is funded by a Meeting and Planning Grant from the Canadian Institutes of Health Research (KPE-126811). The St. Boniface Hospital/I.H. Asper Clinical Research Institute will fund data management, operations and analysis. No site payments are available at the time of writing but funding will be sought.

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Table Legends

Table 1- Delirium Screening Equivalency Table

Table 2- Sedation and Agitation Scales

Appendix

Case Report Form

Delirium Assessment Form

Table 1 – Delirium Screening Equivalency Table

	Intensive Care Delirium Screen Checklist (ICDSC)[1]	Confusion Assessment Method – Intensive Care Unit (CAM-ICU)[2,3]
Onset	Single score of ≥ 4	Single CAM-ICU+ screen
Termination	Three (3) consecutive negative (i.e. 36 hours) ICDSC assessments	Three (3) consecutive negative (i.e. 36 hours) CAM-ICU assessments

Comment [bmc1]: Is there any room for attending clinician to diagnose delirium despite negative screening tool? Should there be?

Comment [A2]: Agree with this definition

Table 2 - Sedation and Agitation Scales

Riker Sedation Agitation Scale (SAS)		Richmond Agitation-Sedation Scale (RASS)	
7 - Dangerous Agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side	+4 - Combative	Overtly combative, violent, immediate danger to staff
6 – Very Agitated	Requiring restraint and frequent verbal reminding of limits, biting ETT	+3 – Very Agitiated	Pulls or removes tube(s) or catheter(s); aggressive
5 - Agitated	Anxious or physically agitated, calms to verbal instructions	+2 - Agitated	Frequent non-purposeful movement, fights ventilator
4 – Calm and cooperative	Calm, easily arousable, follows commands	+1 -Restless	Anxious but movements not aggressive vigorous
3 - Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again	0 – Alert and calm	
2 – Very Sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously	-1 - Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
1 - Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands	-2 – Light Sedation	Briefly awakens with eye contact to voice (<10 seconds)
		-3 – Moderate Sedation	Movement or eye opening to voice (but no eye contact)
		-4 – Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
		-5	No response to voice or physical stimulation

CASE REPORT FORM

Patient initials	_____	
Date of birth	____/_____/_____	
Date of surgery	____/_____/_____	
Procedure	☐ CABG ☐ Valve ☐ CABG+valve ☐ Other	
Sex	☐ Male	☐ Female
Hypertension	☐ Yes	☐ No
Dyslipidemia	☐ Yes	☐ No
Diabetes	☐ Yes	☐ No
Smoking History	☐ Yes	☐ No
COPD	☐ Yes	☐ No
Renal insufficiency	☐ Yes	☐ No
PVD	☐ Yes	☐ No
CVD	☐ Yes	☐ No

Comment [RA1]: What's your definition for renal insufficiency?? e.g. all patients with GFR <60 mL/min/1.73 m^2 for ≥3 months

Comment [AYD2]: Add a list of abbreviations at the beginning

Delirium Assessment

	Shift 1 (i.e. 0700-1500hrs		Shift 2 (i.e. 1500hrs – 2300hrs)		Shift 3 (i.e. 2300hrs – 0700hrs)	
	CAM-ICU/ICDSC	SAS/RASS	CAM-ICU/ICDSC	SAS/RASS	CAM-ICU/ICDSC	SAS/RASS
Day 1						
Day 2						
Day 3						
Day 4						
Day 5						
Day 6						
Day 7						

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.