Contemporary Clinical Trials 39 (2014) 183–190

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Study design of embracing high-sensitivity troponin effectively: The value of more information: A randomized comparison

Carolyn M. Astley [a,*], John F. Beltrame [d], Christopher Zeitz [d], Matthew Worthley [f], Penelope Coates [e], Alistair Murray [b], Margaret Arstall [b], Hugh Grantham [g], Robert Dunn [f], Stephen Quinn [g], Philip E. Aylward [c], Derek P. Chew [c]

[a] SA Health, Flinders University, SA, Australia
[b] Lyell McEwin Hospital, University of Adelaide, SA, Australia
[c] Flinders Medical Centre, SAHMRI, Flinders University, SA, Australia
[d] The Queen Elizabeth Hospital, University of Adelaide, SA, Australia
[e] SA Pathology, SA, Australia
[f] Royal Adelaide Hospital, University of Adelaide, SA, Australia
[g] Flinders University, SA, Australia

ARTICLE INFO

Article history:
Received 23 May 2014
Received in revised form 23 August 2014
Accepted 29 August 2014
Available online 4 September 2014

Keywords:
Pragmatic clinical trial
Measuring innovations
Rigorous methods
Clinical outcomes
Electronic data capture

ABSTRACT

Background: The development of troponin assays with increased diagnostic sensitivity and greater analytic precision has improved the diagnosis of myocardial infarction in high risk patients. However for those patients at intermediate or low risk in whom a small troponin rise is detected, a cascade of clinical decisions and investigations could result; potentially having uncertain impact on recurrent ischemic events and increasing bleeding risk and resource utilization. Clinical equipoise remains as to the clinical utility of high sensitivity troponin.
Methods: We designed a pragmatic randomized clinical trial to evaluate the short and long term clinical impact and resource implications of high sensitivity 5th generation troponin T reporting compared with 4th generation troponin T reporting. Two thousand patients presenting with a suspected acute coronary syndrome were randomized and risk stratified in 5 metropolitan emergency departments in South Australia, Australia. Clinical events occurring after the first 24 h and within 30 days were assessed as the primary endpoint with subsequent events evaluated at 6 and 12 months.
Conclusion: The true translational benefits of innovations in diagnostic testing need to be evaluated in robust clinical trials as they can be costly to introduce and the adoption process often focuses on sensitivity and specificity at the expense of measuring improvements in clinical outcome. The results of this study will provide valuable information on contemporary patterns of troponin utilization on the heterogeneous population of chest pain patients presenting to emergency departments, while providing important information from the clinical practice setting for health administrators, government and policy makers.

1. Introduction

Troponin assays with increased diagnostic sensitivity and greater analytic precision have improved the diagnosis of myocardial infarction (MI) [1,2]. Greater sensitivity of troponin T and troponin I assays has been associated with increased

* Corresponding author at: Flinders Medical Centre, 1 Flinders Dve, Bedford Park, SA 5042, Australia. Tel.:+61 8 8204 6061.
E-mail address: Carolyn.astley@health.sa.gov.au (C.M. Astley).

http://dx.doi.org/10.1016/j.cct.2014.08.012
1551-7144/

identification of patients with MI among patients presenting with undifferentiated chest pain. Greater specificity in the detection of myonecrosis has potentially enabled exclusion of cardiac diagnoses among these patients. However when using high-sensitivity (Hs) assays, detectable elevations in troponin have been associated with increased late mortality among stable angina, heart failure and asymptomatic cohorts [3–5]. Within a relatively high-risk population of patients and using a historical control design, a Hs troponin I assay has been associated with a greater detection of patients with MI and reduced subsequent clinical events within an analysis confined to patients without an established alternative diagnosis [6].

Thus clinical equipoise remains regarding the utility of Hs troponin assays within a broad population representative of routine clinical care. Increased detection of myonecrosis in the emergency department (ED) setting may precipitate a cascade of clinical decisions and investigations with uncertain value on recurrent ischemic events, while potentially increasing the risk of bleeding events and utilization of health care resources. Furthermore, the diagnostic utility of all investigations is dependent on the clinical likelihood of the disease in question. Hence, the implementation of Hs troponin testing at the extremes of diagnostic probabilities may be ineffective and inefficient. Consequently, despite increased clinical adoption, international health technology assessments have highlighted the paucity of adequate comparative evaluations of both Hs troponin I and troponin T assays and do not recommend the change from conventional assays to the Hs assays on the basis of cost-effectiveness [7].

1.1. Objectives

Thus within a randomized comparison, the objectives of this study were to: 1) Use a Hs troponin T (hsTnT) assay to compare troponin reporting ≥5 ng/L to standard (cTnT) reporting ≥30 ng/L on the care of suspected acute coronary syndrome (ACS) patients, on clinical events up to 12-months after presentation. 2) Define the temporal troponin release characteristics associated with subsequent diagnosis of ACS or MI. 3) Validate objectively assessable clinical criteria for determining pre-test probability for evolving ACS. 4) Explore the positive and negative predictive value of Hs troponin at various levels of clinical pre-test probability. 5) Define the relative diagnostic efficiency and cost-effectiveness (as measured by incremental change in health-related quality of life and cost) of applying Hs troponin reporting levels versus existing troponin reporting levels in ACS diagnosis and management.

This article describes the design, methods and value of a novel, pragmatic clinical trial randomizing clinician access to an assay result to evaluate short and long term resource implications of hsTnT reporting compared with cTnT reporting in hospital emergency departments in South Australia (SA), Australia. Uniform testing with hsTnT is used by the SA Pathology Service thus all patients were tested with the hsTnT assay but randomized to receive either a cTnT or hsTnT report. Where a new diagnostic test may be introduced based upon sensitivity and specificity performance comparisons of new versus old, this study controlled access to the test result at a clinical level.

2. Methods

2.1. Design overview

The HsTroponin trial (registered at http://www.ANZCTR.org.au/ ACTRN12611000879965) was a pragmatic, multi-center, randomized, clinical trial (RCT) design. Patients presenting to the ED were randomized to serum troponin levels reported at either 4th generation cTnT standard sensitivity levels (ULN ≥ 30 ng/L) or 5th generation hsTnT high-sensitivity levels (ULN ≥ 5 ng/L). All other subsequent investigations and management were left to the discretion of the clinician. Clinical events occurring after the first 24 h following enrolment and within 30-days were assessed as the primary endpoint with subsequent events evaluated up to 12-months. (Fig. 1). This study is currently completing the follow-up phase.

2.2. Setting and participants

The study included 5 major, metropolitan, public hospital EDs that manage approximately 15,000 chest pain presentations per year from a local population of 1.2 million residents in Adelaide, South Australia (SA), Australia (2011 unpublished data, SA Department of Health). These hospitals are serviced by a common pathology service, thereby ensuring a uniform assay reporting method across the study institutions and facilitating the randomization process.

2.2.1. Inclusion criteria

The study enrolled patients presenting to hospital EDs between July 2011 and March 2013, with clinical features in whom the treating physician sought to measure the serum troponin level, who were over 18 years of age and willing to give his/her written informed consent.

2.2.2. Exclusion criteria

Patients were not eligible to participate in the study if they had persistent ST-segment elevation on the presenting ECG, or unable to complete a clinical history questionnaire due to language barrier or co-morbidity.

2.3. Patient enrolment

Potential study participants fulfilling the above criteria were identified at ED triage and assessed for trial eligibility during initial medical evaluation. Clinical trial nurses, stationed within the ED during weekdays from 9 am–5 pm, were responsible for patient enrolment. Patients were informed of the availability of a newer troponin assay and the uncertainty regarding the clinical relevance of the more sensitive level it reports was explained. Consent was sought before the troponin assay had been processed. Enrolled patients were identified on the pathology request form, together with risk information and forwarded to the centralized pathology service. No management directions were provided to the treating clinicians, however advice regarding the interpretation of the troponin findings was provided by a clinical biochemist if required.