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Is there a clinically meaningful difference in patient reported dyspnea in acute heart failure? An analysis from URGENT Dyspnea

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ABSTRACT

Background: Dyspnea is the most common presenting symptom in patients with acute heart failure (AHF), but is difficult to quantify as a research measure. The URGENT Dyspnea study compared 3 scales: (1) 10 cm VAS, (2) 5-point Likert, and (3) a 7-point Likert (both VAS and 5-point Likert were recorded in the upright and supine positions). However, the minimal clinically important difference (MCID) to patients has not been well established.

Methods: We performed a secondary analysis from URGENT Dyspnea, an observational, multi-center study of AHF patients enrolled within 1 h of first physician assessment in the ED. Using the anchor-based method to determine the MCID, a one-category change in the 7-point Likert was used as the criterion standard ('minimally improved or worse'). The main outcome measures were the change in visual analog scale (VAS) and 5-point Likert scale from baseline to 6-h assessment relative to a 1-category change response in the 7-point Likert scale ('minimally worse', 'no change', or 'minimally better').

Results: Of the 776 patients enrolled, 491 had a final diagnosis of AHF with responses at both time points. A 10.5 mm (SD 1.6 mm) change in VAS was the MCID for improvement in the upright position, and 14.5 mm (SD 2.0 mm) in the supine position. However, there was no MCID for worsening, as few patients reported worse dyspnea. There was also no significant MCID for the 5-point Likert scale.

Conclusion: A 10.5 mm change is the MCID for improvement in dyspnea over 6 h in ED patients with AHF.

Introduction

Patient reported outcomes (PRO) are defined as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patients response by anyone else.'[1] As a measurement of patients' experiences, PRO are key assessments in patient centered research. Dyspnea, or the sensation of breathlessness, is one of the most commonly measured PRO's in acute heart failure (AHF) clinical trials.

The sensation of difficulty breathing or shortness of breath compels patients with AHF to seek medical care.[2,3] Early and persistent relief of dyspnea has been associated with improved outcomes.[4–7] Although dyspnea is significantly improved after initial therapy,[8] a substantial number of patients continue to have

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dyspnea during hospitalization.[4–6] As such, its relief is important to both patients and caregivers, especially with the current focus on patient centered outcomes.[9]

As a subjective, patient reported symptom, how exactly to assess and measure dyspnea continues to be debated.[9–11] While clinical trials now use a more standardized method of dyspnea assessment — formal training, standardized position, only after a period of rest[7] — use of dyspnea as a clinical trial endpoint has fallen out of favor, in part due to the difficulty of demonstrating a significant difference between investigational agents and usual care.[12,13] However, as the predominant AHF symptom, relief from dyspnea is important to patients. Similar to the measurement of pain, proper measurement of dyspnea in AHF is needed.[9]

Unlike COPD or asthma however, how to best measure dyspnea in AHF remains challenging. Which scale to use, when and how often to measure dyspnea lacks convincing data or universal consensus. Furthermore, the accuracy and reliability of such measures continues to be debated.[10] Nevertheless, as the most common presenting symptom in AHF, assessment of dyspnea remains important. Specifically, what degree of improvement is considered a clinically important difference to patients has not been extensively investigated.

The minimal clinically important difference (MCID) is the "smallest benefit of value to patients."[14] As clinicians and patients may disagree on what is clinically meaningful, understanding patients' perspective is critical for a patient centered outcome. Knowing the MCID also informs clinical trial design, providing the minimal effect size. Despite the importance of dyspnea to patients and its near universal presence in AHF patients, the minimal clinically important difference (MCID) in dyspnea via various measurement scales has not been well studied.[7] In our primary paper, we sought to determine changes in dyspnea, using a standardized approach, in ED AHF patients treated with usual therapy.[8] We described the degree of dyspnea improvement in ED patients with AHF and how patient positioning impacted the patients quantification of dyspnea.[8] Briefly, we found most patients (76%) report improvement after 6 h of usual therapy. Furthermore, 47% of patients reported worse symptoms when evaluated lying down compared with sitting upright. Although we found a significant correlation between the 5-point Likert and VAS scales, there was less agreement with the 7-point Likert.[8] Importantly, we did not ascertain the MCID.

Thus, the objective of this paper was to determine the MCID in patients with AHF presenting to the emergency department (ED).

Methods

URGENT Dyspnea was IRB or ethics committee approved at every site. Details regarding the URGENT Dyspnea (Ularitide Global Evaluation in Acute Decompensated Heart Failure) study design and main study results have been previously presented.[8] Briefly, URGENT Dyspnea was a multi-center, prospective observational study that enrolled 776 patients from 17 countries involving 35 sites from January through August of 2007. The primary objective was to determine changes in patient reported dyspnea over 6 h, capturing patients shortly after ED presentation.

At the time of the original study, dyspnea was a major endpoint for every large AHF therapeutic trial. However, how to best measure dyspnea and the time course of its improvement, especially in the ED setting, had not been well studied. At that time, AHF trials were enrolling patients 24–48 h after hospitalization. If dyspnea improved rapidly, capturing patients earlier may be critically important. Thus, our goal was to describe the time course of dyspnea in a broad ED AHF population. Patients were assessed at baseline and then again at 6 h. Six hours was chosen to better capture the time course of dyspnea and also to maintain the study as an ED-based study.

Establishing the MCID

There are multiple techniques to define the MCID; broadly, they may be categorized into three groups: 1) Distribution-based method, 2) Anchor based and the 3) Delphi method. No method has been universally defined as superior to the others. Briefly, the distribution based utilizes the standard deviation or standard error of the mean with a prespecified definition of deviation from the mean as the MCID or a measure at least one standard error away. The anchor based method uses one scale as the anchor for another, different scale. However, establishing what constitutes a MCID on one scale to use as an anchor has been debated. No consensus exists. The final method is a combination of literature review and expert opinion to reach consensus. Although we did not utilize a formal Delphi method, the authors were in consensus regarding the anchor.

Participants

To best replicate 'real-world' conditions, eligibility criteria were intentionally kept broad. Any patient 18 years and older with signs and symptoms of heart failure and the ability to self-assess dyspnea were eligible. However, they had to be enrolled within 1 h of first physician contact. Given the short time frame, patients with dyspnea presumed attributable to AHF were approached, consented, and then enrolled. Treatment and management were directed by the patients' clinical care team: there were no prespecified protocols or treatment interventions. Demographic, clinical, and treatment data were collected per standardized case report form. The site principal investigator, who had full access to all available clinical data, determined the final diagnosis of AHF.

Dyspnea assessment instruments

At 6 h after enrollment, patients were asked about the severity of their dyspnea. They were asked to report via commonly used scales in AHF. The 7-point Likert scale: "Compared to how you felt when you first arrived, do you now feel your breathing is: *Markedly worse, moderately worse, minimally worse, no change, minimally improved, moderately improved, markedly improved?*" We utilized the anchor based method of establishing the MCID, which compares the change in a patient reported outcome to another, different instrument. A one-category change of "minimally worse" or "minimally improved" was used as the criterion standard for the MCID in this study. This standard was chosen based on previously published work in AHF and the MCID,[15] which was based on prior work in the assessment of pain.[15–17]

Two other scales were used to assess dyspnea at both time zero and 6 h later; a 5-point Likert scale ("I am not short of breath (short of breath)", "Mildly short of breath", "Moderately short of breath", "Severely short of breath", "Very Severely short of breath") and a 100 mm VAS, with 0 as "I am not breathless at all" to 100 mm as "I am the most breathless I have ever been." Per protocol, this 100 mm line was divided into 10 equal 1 cm increments and scored accordingly. Patients were specifically asked: "How short of breath do you feel?" prior to their response.

Despite each of these instruments being used in AHF clinical trials,[7,13,18–21] their reliability and validity in the setting of AHF has not been well studied.[9,22] This actually led to the design and conduct of the primary URGENT Dyspnea study.[8] Our own work suggests potentially significant differences in response between