Treatment of new-onset atrial fibrillation in noncardiac intensive care unit patients: A systematic review of randomized controlled trials*

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Objective: Atrial fibrillation is a common problem associated with morbidity and mortality in critically ill patients; however, evidence-based treatment recommendations are lacking. The objective of this systematic review was to evaluate the efficacy of pharmacologic rhythm control of new-onset atrial fibrillation in noncardiac, critically ill adults.

Data Source: Citations identified from an electronic search of Medline, the Cochrane register of controlled trials, and Embase databases (1966 to August 2006) were independently reviewed by two investigators.

Study Selection: All prospective randomized controlled trials evaluating pharmacologic rhythm conversion regimens for new-onset atrial fibrillation in (noncardiac surgery) critically ill adult patients were included. The primary end point was atrial fibrillation resolution.

Data Extraction: Using a standardized data extraction form, data related to study design, population characteristics, pharmacologic intervention, and outcome measures were collected.

Data Synthesis: Four trials met inclusion criteria from 1995 citations screened. Of the 143 evaluable patients in these trials 89 (76%) had atrial fibrillation while the remaining ones had other atrial tachyarrhythmias. Drugs evaluated for rhythm conversion included amiodarone (n = 26), procainamide (n = 14), magnesium (n = 18), flecainide (n = 15), esmolol (n = 23), verapamil (n = 15), and diltiazem (n = 27). The definition of treatment success ranged from conversion within 1 hr to conversion within 24 hrs. No study evaluated maintenance of conversion, and one study included hemodynamically unstable patients. Lack of methodologic homogeneity prevented any pooled analysis.

Conclusions: Using the current published literature, we cannot recommend a standard treatment for atrial fibrillation in noncardiac critically ill adult patients. Clinical trials evaluating rhythm conversion in critically ill populations outside of cardiac surgery are lacking. Further trials that address goals of care in hemodynamically stable and unstable patients and utilize standardized definitions of successful cardioversion are required. (Crit Care Med 2008; 36:1620–1624)

Key Words: atrial fibrillation; supraventricular arrhythmia; intensive care; critical care; systematic review

Atrial fibrillation is the most common dysrhythmia among intensive care unit (ICU) adult patients (1, 2). In the critically ill surgical population, new-onset atrial fibrillation is most common after cardiac surgery (10–65%) (3), followed by thoracic surgery (10–23%) (4–11), and nonthoracic surgery (5–10%) (1, 12–14). In the critically ill medical population, the prevalence of new-onset atrial fibrillation appears to range from 10 to 20% (15–17).

A relationship between new-onset atrial fibrillation and morbidity/mortality has been described in the critically ill patient. Following cardiac surgery, the development of atrial fibrillation is associated with a 2- to 2.5-fold increase in the risk of death in hospital and at 6 months, while this risk has been reported to be two- to six-fold higher after noncardiac surgery (1, 6, 11, 14, 18). Only one single-center study reports a doubling of the risk of death in medical ICU patients who develop new-onset atrial fibrillation (15). While this association between new-onset atrial fibrillation in the ICU and mortality has not been well described, it has been suggested that atrial fibrillation may simply be a marker of severity of illness rather than an independent contributor of mortality.

In most cases, atrial fibrillation is a transient phenomenon with a reversible underlying cause (i.e., electrolyte disturbances, dramatic fluid shifts, hyperadrenergic states, etc.). However, the underlying cause may often be multifactorial and not immediately reversible in a critically ill population. The efficacy of pharmacologic prophylaxis and treatment of atrial fibrillation after cardiac surgery has been evaluated in many studies leading to the recent publication of clinical practice guidelines in this population (19, 20). On the other hand, optimal treatment of atrial fibrillation in medical and (noncardiac) surgical ICU populations is ill-defined despite a prevalence and morbidity similar to those of the cardiac surgery population. The objective of this project...
was to evaluate the existing evidence for pharmacologic rhythm conversion for new-onset atrial fibrillation in noncardiac critically ill adults. Therefore, we conducted a systematic review of published clinical trials comparing the effect of drug treatment regimens in this population.

METHODS

Search Strategy. We conducted a systematic search of Medline, Cochrane, and Embase databases from 1966 until August 2006 to identify randomized controlled trials evaluating the effect of pharmacologic treatment of new-onset atrial fibrillation in critically ill patients. Only peer-reviewed trials published in English language were considered eligible for this review. Databases were searched using a combination of the following terms: “atrial fibrillation,” “atrial flutter,” “supraventricular arrhythmia,” “tachyarrhythmia,” “critical care,” and “intensive care” with the Dickersin filter for randomized controlled trials (21). The search also incorporated text words for drugs including “disopyramide,” “procainamide,” “quinidine,” “lidocaine,” “mexilitine,” “phenytoin,” “tocainide,” ”flecainide,” “moricizine,” “propafenone,” “amiodarone,” “sotalol,” “ibutilide,” “dofetilide,” “bretylium,” “esmolol,” “propranolol,” “metoprolol,” “diltiazem,” and “verapamil.” Reference lists of review articles and included studies were also screened for additional studies. Two experienced practitioners (SK and RS) independently reviewed all citations retrieved from the electronic search to identify potentially relevant trials.

Study Selection. All randomized controlled trials comparing a pharmacologic therapy to an inert or an active control for new-onset atrial fibrillation in critically ill adult patients were included in this systematic review. New-onset atrial tachyarrhythmias were defined as atrial fibrillation, atrial flutter, or other supraventricular tachyarrhythmias of less than 7 days duration. Continuous electrocardiography monitoring was required during the study period. Patients had to be critically ill, defined as being admitted to an ICU, and be more than 16 yrs of age. Studies in cardiac surgery patients or on patients treated before ICU admission were excluded. The primary outcome measure was rhythm conversion to normal sinus rhythm of any duration.

Data Extraction and Validity Assessment. Using a standardized data extraction form, data related to study design, population characteristics, pharmacologic intervention, and outcome measures were collected. Discrepancies of data interpretation were resolved by consensus among investigators. Attempts were also made to acquire additional information from study investigators when possible. Quality assessment of each study was conducted using the rating instrument developed by Jadad et al (22). This instrument evaluates clinical trial integrity based on methods of randomization, blinding and documentation of withdrawals from the study. Scores for each section of the instrument were determined and reported individually. A maximum score of 5 would be awarded to a trial with the greatest methodologic integrity (i.e., appropriately described randomization procedure and double blinding with description of withdrawals from the study). We considered trials with a score of 3 or higher to be of high-methodologic quality.

Data Synthesis. Data related to study design, drug treatment, patient demographics, and outcome measures including conversion rates as defined by the trials, time to conver-
sion, arrhythmia recurrence rates, and adverse events were described for individual studies identified. Pooled estimates of outcome measures were not calculated due to study heterogeneity, therefore, forest plots without pooled estimates are presented.

RESULTS

Search Results and Description of Studies. From 1995 citations screened, 44 were evaluated and four trials (n = 143) were included in the analysis (23–26). (Fig. 1). Two trials included a mixed population of surgical and medical patients (25, 26) while the remaining two were performed in a strict medical population (24) and a surgical population (23). While all studies excluded patients after cardiac surgery, one trial included three patients post-thoracotomy (26) and one enrolled 15 patients post-thoracic surgery (23). Of the 143 evaluable patients, 89 (76%) had atrial fibrillation while the remaining had other atrial tachyarrhythmias. All trials evaluated the success of cardioversion. The definition of success ranged from rhythm conversion within 1 hr to conversion within 24 hrs (Table 1). The antiarrhythmic drugs evaluated included amiodarone (two trials, n = 26), procainamide (one trial, n = 14), magnesium (one trial, n = 18), and flecainide (one trial, n = 15), while the chronolytic drugs evaluated include esmolol (one trial, n = 28), verapamil (one trial, n = 15), and diltiazem (one trial, n = 27). One trial included hemodynamically unstable patients (23).

Methodologic Quality. One trial was considered to be of high methodologic quality (26). All trials were randomized comparator control trials; however, only one trial described an appropriate method of randomization (26). None of the trials were blinded. One trial (23) described an intention-to-treat analysis and no trial collected data beyond 24 hrs, thus no patients were lost to follow-up.

Outcomes. Rhythm conversion was defined by a different metric in each trial ranging from conversion within 1 hr to conversion within 24 hrs. Maintenance of rhythm control was not evaluated in any study. The two studies that evaluated rhythm conversion with amiodarone reported success rates of 50–70% at 12 hrs and 50% at 24 hrs (25, 26). Chapman et al. observed similar success rates of amiodarone use when compared to procainamide (70 vs. 71%) at 12 hrs for amiodarone and procainamide, respectively; p = not significant) (25). Moran et al. reported a higher conversion rate with magnesium at 24 hrs (77%) when compared to amiodarone (50%, p value not reported) (26). Most patients in these two trials also received digoxin for rate control purposes. In the study by Barranco et al., the primary outcome of conversion to normal sinus rhythm within 1 hr occurred in 80% of patients receiving flecainide and 33% of those receiving verapamil (p < .001) (24). The authors concluded that flecainide was an effective agent for the conversion of atrial tachyarrhythmias to normal sinus rhythm. Finally, the study by Balser et al. compared the frequency of rhythm conversion within 12 hrs between two pharmacologic interventions (diltiazem and esmolol) traditionally considered as rate control agents (23). Conversion rates with esmolol were higher than those of diltiazem at 2 hrs (68% vs. 33%, p < .05) and at 12 hrs (85% vs. 62%, p = .116). Both agents were equally effective for rate control of rapid atrial arrhythmias. Conversion rates are summarized in Figure 2.

Safety was evaluated in all studies. Among the 24 patients randomized to receive amiodarone, two patients experienced clinically significant hypotension and two others died before trial completion. The cause of death in these two patients was not described by the authors. Treatment with flecainide (n = 15) was associated with a significant prolongation of the QRS interval resulting in frequent premature ventricular contractions in one patient and brief episodes of hypotension in two patients, none of which required interruption of the infusion. Hypotension was observed in three patients treated with verapamil (n = 15), ten patients treated with esmolol (n = 34) and 12 patients treated with diltiazem (n = 30). Hypotension was most often observed during the loading dose and was self-limited. Discontinuation of the study drug was only necessary in two patients receiving esmolol and one patient receiving diltiazem.

DISCUSSION

This systematic review of clinical trials evaluating the effect of pharmacologic treatment on rhythm conversion of new-onset atrial fibrillation in noncardiac critically ill patients yielded only four trials of which 89 subjects enrolled had atrial

Table 1. Study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial Design</th>
<th>Blinding</th>
<th>Patients</th>
<th>N</th>
<th>Intervention</th>
<th>Patients with AF</th>
<th>Definition of Cardioversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman (1993)</td>
<td>Randomized controlled</td>
<td>No</td>
<td>Med/surg</td>
<td>24</td>
<td>Amiodarone (3 mg/kg bolus then 10 mg/kg over 24 hrs) vs. procainamide (10 mg/kg bolus then 4 mg/min × 2 hrs, then 3 mg/kg × 2 hrs then 2 mg/kg × 20 hrs)</td>
<td>16/24</td>
<td>Within 12 hrs</td>
</tr>
<tr>
<td>Moran (1995)</td>
<td>Randomized controlled</td>
<td>No</td>
<td>Med/surg</td>
<td>42 (34 evaluable)</td>
<td>Amiodarone (5 mg/kg bolus then 10 mg/kg over 24 hrs) vs. magnesium (37 mg/kg bolus, then 25 mg/kg/hr × 24 hrs)</td>
<td>18/34</td>
<td>Within 24 hrs</td>
</tr>
<tr>
<td>Barranco (1994)</td>
<td>Randomized controlled</td>
<td>No</td>
<td>Med</td>
<td>30</td>
<td>Flecainide (2 mg/kg bolus then 1.5 mg/kg over 1 hr) vs. verapamil (0.15 mg/kg bolus then 0.005 mg/kg/min × 1 hr)</td>
<td>11/30</td>
<td>Within 1 hr</td>
</tr>
<tr>
<td>Balzer (1998)</td>
<td>Randomized controlled</td>
<td>No</td>
<td>Surg</td>
<td>55</td>
<td>Esmolol (12.5–50 mg repeated bolus until HR &lt;110 beats/min then 50–100 µg/min) vs. diltiazem (20 mg bolus then 10–20 mg/hr)</td>
<td>44/55</td>
<td>Within 12 hrs</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>143</td>
<td></td>
<td>89/143 (76%)</td>
<td></td>
</tr>
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HR, heart rate; AF, atrial fibrillation.
fibrillation. While all the trials identified evaluated rhythm conversion as their primary outcome measure, considerable heterogeneity related to patient selection, definitions of outcome measures, and duration of study was observed, limiting our ability to make a generalizable statement about pharmacologic rhythm conversion in this population. Little evidence exists that describes superior efficacy of one drug over another or even one drug over placebo. Thus, based on the current literature, we cannot recommend evidence-based standards regarding both goals of treatment and intervention selection in critically ill adult patients with new onset atrial fibrillation.

A comparable systematic review was recently conducted evaluating pharmacologic rhythm conversion of atrial fibrillation after cardiac surgery (19). This review identified 19 randomized controlled trials evaluating a variety of antiarrhythmic drugs. Similar limitations of the included trials were identified by the authors including heterogeneity between trials with respect to subject outcomes, outcome measures, and monitoring methods. Due to this heterogeneity and subsequent highly variable conversion rates, no pharmacologic strategy was identified as superior to another. For comparison, conversion rates were 13 to 100% in four trials of amiodarone, 51 to 93% in two trials of procaïnamide, 86 to 93% in two trials of flecainide, and 7 to 55% in two trials of diltiazem. Of note, two trials reported conversion rates of 24 and 16% for placebo. Conversion rates for the common drugs in the current systematic review were at least similar to conversion rates reported in the cardiac surgery systematic review.

In comparison, direct current cardioversion may be an attractive alternative to pharmacologic rhythm control. This is especially true for the patient with new-onset atrial fibrillation and deteriorating hemodynamics where prompt restoration of sinus rhythm is essential and avoiding pharmacologic exacerbation of hypotension is pivotal. In noncritically ill patients direct current cardioversion has been described as a highly effective therapy with rates of successful restoration of normal sinus rhythm as high as 70 to 95% (27–29). However, only one prospective observational study of monophasic direct current cardioversion in 37 surgical ICU patients reports a successful initial conversion rate of 35% and only 13.5% at 48 hrs (30).

Considering the prevalence of atrial arrhythmias in the noncardiac critically ill patient and the associated morbidity and mortality, there are very few prospective randomized trials designed to evaluate the treatment of this condition. One reason that could explain the paucity of research in this area is the difficulty in conducting clinical trials in these patients. Because new-onset atrial fibrillation with a rapid ventricular rate is considered an emergency, enrolling these patients into clinical trials is logistically difficult as rapid intervention may be desired.

The limitations of this systematic review are related to the included primary studies. Differences in the baseline study populations might have lead to different treatment effects since all studies included subjects with a variety of atrial arrhythmias. While cardiac surgery patients were excluded, two trials enrolled thoracic surgery patients. Furthermore, three of the four clinical trials excluded patients who were hemodynamically unstable. Grouping atrial fibrillation with atrial flutter and supraventricular tachycardias might also be inappropriate as the primary physiology behind them and their treatment response might be different (15). The study by Balser et al. was the only study to evaluate hemodynamically unstable patients. Given the potential consequences of hemodynamic instability in a critically ill patient, the goal of care in this population would be rhythm conversion presumably to restore the atrial kick and improve cardiac output. On the other hand, rhythm control might be unnecessary if rate control can be achieved while the underlying disease is managed. One could argue that if rate control is the goal of care, conversion without an antiarrhythmic agent would represent spontaneous conversion. However, as hypothesized in the study by Balser et al., beta adrenergic blockade alone may have antiarrhythmic activity in the setting of adrenergic-induced atrial arrhythmogenicity.

The second major limitation of the studies included in this review relates to the lack of standardized outcome measures. The definition of successful cardioversion ranged from conversion within one hour to conversion within 24 hrs, but no study evaluated maintenance of conversion. Since the etiology of atrial fibrillation in the critical care setting is often attributed to reversible causes that may not be immediately corrected, many patients will relapse into atrial fibrillation after presumably successful rhythm conversion. Such discrepancy in the definition of the primary outcome prevents any recommendation on treatment efficacy. Moreover, from the trials evaluated in this systematic review it is impossible to differentiate drug efficacy from spontaneous conversion. A standardized definition of rhythm conversion that incorporates a means to evaluate maintenance of normal sinus rhythm after conversion would be needed for further trials.

In summary, well-designed randomized controlled trials evaluating rhythm conversion in critically ill adult patients outside of cardiac surgery care are lacking. Only four prospective studies were identified and their interpretation was limited by considerable methodologic heterogeneity. While antiarrhythmic agents such as amiodarone, magnesium, procaïnamide, and flecainide are all described as effective agents to varying degrees, it is difficult to differentiate the efficacy of the drug from spontaneous conversion. Future studies should address treatments of choice and goals of care using a standardized outcome measure of success. Properly designed, adequately powered prospective clinical trials are required.

REFERENCES