The haemodynamic changes associated with treatment of new-onset atrial fibrillation with amiodarone or beta blockers

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Abstract

Amiodarone and beta blockers are common treatments for new-onset atrial fibrillation (NOAF) in patients treated on an intensive care unit (ICU). How these treatments affect patients' haemodynamic status is unclear, yet purported differences often affect clinicians' treatment choice.

We undertook a multicentre observational study of ICUs in one United States of America (USA) centre and two United Kingdom (UK) centres to explore the changes in blood pressure and cardiovascular support associated with amiodarone or beta blocker therapy for NOAF.

We identified 2017 patients who developed NOAF during their ICU stay, of which 958 were treated with amiodarone or beta blockers as first line therapy.

Neither amiodarone nor beta blockers were associated with significant changes in blood pressure over the 3h post-treatment initiation (amiodarone mean blood pressure (MBP +0.04mmHg/h, p = 0.90 and systolic blood pressure (SBP) +0.11mmHg/h, p = 0.83; beta blocker MBP -0.41mmHg/h, p = 0.17 and SBP -0.15mmHg/h, p = 0.75). Amiodarone was associated with a very slight increase in vasoactive medication use. In a subgroup of patients with lower blood pressures, amiodarone was associated with a slight improvement in blood pressure (+1.36mmHg/h, p = 0.02), whereas beta blocker therapy was not associated with any change (+0.24mmHg/h, p = 0.72).

These data do not support the commonly held belief that beta blockers result in hypotension or increased vasoactive medication requirements when used for NOAF treatment within an ICU. These findings from observational data need investigating in well-designed randomised trials.

Keywords

Intensive care
Critical illness
Arrhythmia
Atrial fibrillation
Circadian rhythm

1 INTRODUCTION

New-onset atrial fibrillation (NOAF) is a common complication of critical illness, occurring in around 15% of ICU admissions[1]. Incidence is higher in certain patient groups, such as those with sepsis[2]. NOAF during critical illness is associated with increased ICU and hospital mortality, and increased length of ICU and hospital stay[1,3]. NOAF during critical illness appears to carry a long-term burden, increasing the risk of future readmissions with heart failure or stroke, and worsening 5-year survival[4].

Guidelines exist for management of AF in patients in the community. However, There is a little evidence for AF management in the critically ill, where risks and benefits with different treatments are unclear[5]. There is significant variation within and between UK ICUs in the management of NOAF, with amiodarone the most commonly used medication[6] Amiodarone is often stated to result in haemodynamic instability than alternatives such as beta blockers or calcium channel blockers[7], and this may explain its preferred use in the UK.

Amiodarone infusion is associated with a reduction in blood pressure[8,9]. Whilst this effect may be more marked with calcium channel blockers[10], a comparison with beta blockers has not been made. Use of beta blockers for NOAF management may be associated with lower in-hospital mortality compared with CCBs, digoxin, or amiodarone in patients with sepsis[11]. Furthermore, the use of beta blockers during sepsis may improve ventricular-arterial coupling[12] and was associated with reduced mortality in a single-centre study[13].

In light of these potential benefits, the use of beta blockers in NOAF management in critically ill patients required further study.

2 METHODS

2.1 STUDY DESIGN

We undertook a retrospective observational study of two ICU databases (MIMIC-III and PICRAM) to explore the timing of NOAF. PICRAM [14] contains data from >12,000 patients treated on three general UK ICUs between 2008 and 2015. MIMIC-III v1.4 [15] comprises data from >40,000 patients admitted to ICUs between 2001 and 2012 at one tertiary care hospital in the USA.

2.2 PARTICIPANTS

We included the first ICU admission of all adult (≥16 years) patients. We excluded patients: cared for by a coronary care or cardiac surgery team, admitted for less than 24 hours, or with pre-existing arrhythmias (either documented in their medical history, or recorded in the first three hours of arrival to ICU as a surrogate for undocumented pre-existing arrhythmia).

2.3 OUTCOMES

Our primary outcomes were the change in mean blood pressure (MBP), systolic blood pressure (SBP) and vasoactive-inotropic score from baseline (time of NOAF treatment initiation) to 3 hours post-baseline.

Our secondary outcomes were change in blood pressure and vasoactive-inotropic score[16] (VIS) from baseline to 12 hours post-baseline, and the proportion of patients receiving cardiovascular support before and after NOAF treatment.

2.4 STATISTICAL METHODS

We used smooth additive quantile (25%, 50%, 75%) regression models to visualise changes in mean blood pressure (MBP) systolic blood pressure (SBP), proportion of patients receiving vasoactive

mediations and VIS (in patients receiving vasoactive at the time of NOAF treatment) during the 3 hours before and 12 hours after NOAF treatment[17]. We used mixed-effects linear models to compare mean changes in haemodynamic variables over the first 3 and 12 hours after treatment. We included random intercepts/slopes per patient. We used a Chi-squared test to compare the proportion of patients receiving cardiovascular support in the 3h pre- and post-NOAF treatment.

We also analysed our primary outcomes in a subgroup of patients who had mean arterial pressures (MAP) <70mmHg[18] throughout the 2 hours prior to treatment initiation

3 RESULTS

After exclusions, the study cohort comprised 2,017 patient admissions, of which 1,065 were from the MIMIC-III database and 952 from PICRAM (Figure 1).

Of the 2,017 patients who developed NOAF during their ICU stay, 958 were treated with amiodarone or beta blockers (438 and 520, respectively). Whilst patients in both groups had similar illness severity at admission, patients who received amiodarone tended to have lower blood pressures and were more likely to be receiving vasoactive medications after AF onset, before treatment (Table 1)

3.1 PRIMARY OUTCOMES

From the start of treatment to 3h post-treatment, neither amiodarone nor beta blockers were associated with a significant change from baseline in MBP nor SBP in multilevel models (amiodarone MBP +0.04mmHg/h, p = 0.90 and SBP +0.11mmHg/h, p = 0.83; beta blocker MBP -0.41mmHg/h, p = 0.17 and SBP -0.15mmHg/h, p = 0.75).

In those patients receiving vasoactive medications prior to NOAF treatment (n = 190), amiodarone therapy was associated with a slight increase in VIS (+0.65 points/h, p = 0.049), whereas beta blocker therapy was not associated with any change in VIS (-0.27 points/h, p = 0.59). There was no change in

the proportion of patients receiving vasoactive medications before and after treatment in either treatment group (amiodarone 0.33 to 0.34, p = 0.98; beta blockers 0.11 to 0.10, p = 0.58). Distributions of haemodynamic variables are shown in Figure 2.

In the subgroup of patients with MAP <70mmHg prior to NOAF treatment (n = 171, amiodarone n = 99, beta blocker n = 72) amiodarone therapy was associated with a slight increase in MBP after treatment (+1.36mmHg/h, p = 0.02), whereas beta blocker therapy was not associated with any change (+0.24mmHg/h, p = 0.72). These findings were consistent across SBP (amiodarone +2.2mmHg/h, p = 0.01; beta blockers +1.2mmHg/h, p = 0.25). In this subgroup, neither amiodarone nor beta blockers were associated with any change in VIS from baseline over the first 3h (amiodarone +0.24 points/h, p = 0.65; beta blockers -0.1points/h, p = 0.92). There was no change in the proportion of patients receiving vasoactive medications before and after treatment in either treatment group (amiodarone 0.48 to 0.51, p = 0.78; beta blockers 0.22 to 0.21, p = 0.98). Distributions of haemodynamic variables in this subgroup are shown in Figure 3.

3.2 SECONDARY OUTCOMES

From the start of treatment to 12h post-treatment, amiodarone was associated with a very slight increase in MBP and SBP (+0.17mmHg/h, p = 0.01 and +0.66mmHg, p<0.001, respectively). Beta blockers were not associated with any increase in MBP (-0.06mmHg/h, p = 0.38), but a very slight increase in SBP (+0.26mmHg/h, p = 0.006). Over this timeframe, amiodarone was associated with a slight reduction in vasoactive medication use (-0.3points/h, p = 0.004), whereas beta blockers were not associated with any change (-0.26 points/h, p = 0.13).

Table 1 - Characteristics of included patients

Characteristic	Amiodarone, N = 438	Beta blockers, N = 520	Overall, N = 958
Database			
-MIMIC-III	94 (21%)	473 (91%)	567 (59%)
-PICRAM	344 (79%)	47 (9.0%)	391 (41%)
Age	69 (63, 78)	73 (64, 82)	71 (63, 80)
Sex			
-F	192 (44%)	254 (49%)	446 (47%)
-M	246 (56%)	266 (51%)	512 (53%)
COPD	54 (12%)	29 (5.6%)	83 (8.7%)
NYHA class III/IV heart failure	2 (0.5%)	0 (0%)	2 (0.2%)
Dialysis-dependent renal failure	6 (1.4%)	1 (0.2%)	7 (0.7%)
Chronic liver disease	16 (3.7%)	8 (1.5%)	24 (2.5%)
Thyroid disorder	23 (5.3%)	30 (5.8%)	53 (5.5%)
Beta blocker therapy prior to admission	82 (19%)	203 (43%)	285 (32%)
Antipsychotic medication prior to admission	9 (2.1%)	20 (4.2%)	29 (3.2%)
Highest OASIS Score at 3h	35 (28, 41)	35 (30, 40)	35 (29, 40)
Mechanical ventilation at time of NOAF	252 (58%)	228 (44%)	480 (50%)
Renal replacement therapy during or <12h prior to NOAF	57 (13%)	43 (8.3%)	100 (10%)
IV Vasoactive medication at time of NOAF	139 (32%)	51 (9.8%)	190 (20%)
Therapeutic anticoagulation at time of NOAF	43 (9.8%)	28 (5.4%)	71 (7.4%)
Central venous catheter at time of NOAF	331 (76%)	293 (56%)	624 (65%)
Bronchodilator therapy on day of, or day preceding, NOAF	90 (21%)	162 (31%)	252 (26%)
Plasma sodium concentration (mmol/L)	137 (134, 141)	139 (137, 143)	138 (135, 142)
Plasma potassium concentration (mmol/L)	4.2 (3.9, 4.5)	4.0 (3.7, 4.4)	4.1 (3.8, 4.5)
Plasma magnesium concentration (mmol/L)	0.92 (0.81, 1.08)	0.86 (0.78, 0.95)	0.86 (0.78, 1.01)
Plasma urea concentration (mmol/L)	12.7 (8.4, 19.2)	8.9 (6.1, 16.1)	11.1 (6.5, 17.8)
Plasma creatinine concentration (micromol/L)	120 (76, 217)	97 (62, 159)	106 (68, 192)
White cell count (x109 / L)	11.6 (7.6, 16.9)	11.6 (8.8, 15.5)	11.6 (8.2, 16.1)
Haemoglobin concentration (g/L)	98 (87, 111)	103 (92, 115)	101 (89, 114)
Platelet count (x109 / L)	165 (102, 242)	190 (126, 283)	178 (116, 263)
Prothrombin time	16.0 (14.9, 19.0)	14.2 (13.2, 16.3)	15.2 (13.6, 18.0)
Systolic blood pressure after AF onset	110 (96, 126)	119 (104, 141)	116 (101, 134)
Mean blood pressure after AF onset	74 (66, 85)	80 (69, 92)	77 (68, 89)
Heart rate after AF onset	128 (108, 147)	121 (103, 136)	124 (106, 141)

4 CONCLUSION

Our findings suggest that amiodarone tends to be used in more haemodynamically unstable patients that beta blockers. However, in our primary analysis we did not find any evidence to support a differential effect on blood pressure between these two treatments. In patients with lower blood pressures, amiodarone may promote a slightly faster resolution in blood pressure. We found no evidence that beta blocker therapy results in blood pressure reduction or an increase in vasoactive medications. These findings require further study in the context of randomised trials.

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LIST OF ABBREVIATIONS

NOAF: New-onset atrial fibrillation
AF: Atrial fibrillation
ICU: Intensive Care Unit

DECLARATIONS

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Conflicts of interest/Competing interests

Peter Watkinson worked for Sensyne Health and has received grant funding from the National Institute for Health Research, Wellcome, and Sensyne Health outside the submitted work

Availability of data and material (data transparency)

MIMIC-III is an openly available dataset (details at https://mimic.physionet.org/). The PICRAM dataset is not currently publicly available.

Code availability

Not applicable

Ethics approval and consent to participate

The PICRAM study was granted ethical approval by the NRES Committee Oxford (ref:11/SC/0440) and the National Information Governance Board (ref: ECC 7–05(f)/2011).

Consent for publication

Not applicable

Authors' contributions

JB and OR conceived the study, extracted data, performed statistical analysis, and co-wrote the manuscript. AJ extracted data from the MIMIC-III database, and synthesised data from both databases. KR provided expert review and advice and co-wrote the manuscript. Peter Watkinson contributed to study conception, design and co-wrote the manuscript.

FIGURE CAPTIONS

Fig. 1 Study flowchart

Fig. 2 Haemodynamic changes associated with NOAF treatment with amiodarone (panel A) and beta blockers (panel B). Vasoactive-inotropic score (VIS) shown for those patients receiving vasoactive medications prior to AF onset. VIS = Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 x Epinephrine dose (mcg/kg/min) + 10 x Milrinone dose (mcg/kg/min) + 10,000 x Vasopressin dose (units/kg/min) + 100 x Norepinephrine dose (mcg/kg/min)

Fig. 3 Haemodynamic changes associated with NOAF treatment in patients with MAP <70 prior to treatment with amiodarone (panel A) and beta blockers (panel B). Vasoactive-inotropic score (VIS) shown for those patients receiving vasoactive medications prior to AF onset. VIS = Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 x Epinephrine dose (mcg/kg/min) + 10 x Milrinone dose (mcg/kg/min) + 10,000 x Vasopressin dose (units/kg/min) + 100 x Norepinephrine dose (mcg/kg/min)