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Journal club critique

Due caution using early β-blockers for acute myocardial infarction

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Expanded Abstract

Citation

Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1622-1632 [1].

Background

Despite previous randomised trials of early β-blocker therapy in the emergency treatment of myocardial infarction (MI), uncertainty has persisted about the value of adding it to current standard interventions (e.g., aspirin and fibrinolytic therapy), and the balance of potential benefits and hazards is still unclear in high-risk patients.

Methods

Design and setting: Prospective blinded randomized controlled trial in 1250 hospitals in China.

Subjects: 45,852 patients admitted within 24 h of suspected acute MI onset. 93% had ST-segment elevation or bundle branch block, and 7% had ST-segment depression.

Intervention: Subjects were randomly allocated metoprolol (up to 15 mg intravenous then 200 mg oral daily; n=22,929) or matching placebo (n=22,923). Treatment was to continue until discharge or up to 4 weeks in hospital (mean 15 days in survivors) and 89% completed it.

Outcomes: The two pre-specified co-primary outcomes were: (1) composite of death, reinfarction, or cardiac arrest; and (2) death from any cause during the scheduled treatment period. Comparisons were by intention to treat, and used the log-rank method. This study is registered with ClinicalTrials.gov, number NCT 00222573.

Results: Neither of the co-primary outcomes was significantly reduced by allocation to metoprolol. For death, reinfarction, or cardiac arrest, 2166 (9.4%) patients allocated metoprolol had at least one such event compared with 2261 (9.9%) allocated placebo (odds ratio [OR] 0.96, 95% CI 0.90–1.01; p=0.1). For death alone, there were 1774 (7.7%) deaths in the metoprolol group versus 1797 (7.8%) in the placebo group (OR 0.99, 0.92–1.05; p=0.69). Allocation to metoprolol was associated with fewer people having reinfarction (464 [2.0%] metoprolol *vs.* 568 [2.5%] placebo; OR 0.82, 0.72–0.92; p=0.001) and ventricular fibrillation (581 [2.5%] *vs.* 698 [3.0%]; OR 0.83, 0.75–0.93; p=0.001). Overall, these reductions were counterbalanced by more subjects developing cardiogenic shock (1141 [5.0%] *vs.* 885 [3.9%]; OR 1.30, 1.19–1.41; p<0.00001). This excess of cardiogenic shock was mainly during days 0–1 after admission, whereas the reductions in reinfarction and ventricular fibrillation emerged more gradually. Consequently, the overall effect on death, reinfarction, arrest, or shock was significantly adverse during days 0–1 and significantly beneficial thereafter. There was substantial net hazard in hemodynamically unstable patients, and moderate net benefit in those who were relatively stable (particularly after days 0–1).

Conclusion

The use of early β-blocker therapy in acute MI reduces the risks of reinfarction and ventricular fibrillation, but increases the risk of cardiogenic shock, especially during the first day or so after admission. Consequently, it might generally be prudent to consider starting β-blocker therapy in hospital only when the hemodynamic condition after MI has stabilized.

Commentary

β-blockers are a fundamental therapeutic tool in the management of many conditions seen in ICU patients, including hypertension, aortic dissection, and various arrhythmias/tachycardias. Based on American Heart Association emergency cardiac care guidelines [2], both IV and oral β-blockers are often utilized for initial management of acute MI. The potential benefits of early therapy are well understood, and include reduced risks for ventricular fibrillation and reinfarction. Long-term oral therapy is associated with a number of benefits including secondary prevention, reduced mortality, and improved left ventricular function.

The evidence base for early β-blocker use was generated mostly in the pre-thrombolytic era and use has been perpetuated by practice guidelines [2,3]. The current study, COMMIT/CCS-2 [1], appropriately re-addressed the question of whether β-blocker use is still appropriate under contemporary conditions, which include access to thrombolytics, rapid percutaneous coronary intervention, emergent cardiac bypass, adjuncts such as intra-aortic balloon pumps, and well-established medical therapies, such as aspirin and angiotensin converting enzyme inhibitors.

In the present study, 45,852 subjects were randomized to IV followed by oral metoprolol or matching placebo within 24 h of onset of a suspected acute MI. The study included a mix of low risk, moderate risk, and high risk patients, but excluded those undergoing percutaneous coronary interventions. The groups were well-balanced at baseline. Compliance and follow-up were excellent.

Surprisingly, there were no differences between groups for the co-primary outcomes of: (1) composite of death, reinfarction, or cardiac arrest; and (2) death from any cause during the scheduled treatment period. The finding of no mortality benefit associated with early metoprolol treatment was driven by two opposing effects: increased risk of cardiogenic shock in days 0-1 with an offsetting reduction in ventricular fibrillation and reinfarction that occurred later in the hospital stay. These biologically plausible findings can at least partially be explained by the inclusion of high risk subjects, such as those presenting with pulmonary congestion. However, even among patients with hypertension, tachycardia, or Killip class 1 status (individuals with no clinical signs of heart failure), there was a greater risk of cardiogenic shock with metoprolol, suggesting that even these individuals do not universally tolerate early β-blockade.

A few limitations of this study warrant consideration. It is common practice to use oral doses of metoprolol that are much less than the 50 mg every 6h that was employed in COMMIT/CCS-2. Furthermore, the initial IV doses were given at relatively frequent intervals, every 2-3 minutes over a 2-3 minute period. Customizing the approach, either by waiting longer between IV doses or by using a lower subsequent oral dose, might help limit progression to drug-associated cardiogenic shock. Because this study focused on subjects presenting with acute MI, care providers should use caution in extrapolating these results to the management of acute MI occurring in patients already admitted to an ICU for other reasons. Many of these patients (surgical or otherwise) have contraindications to therapies, such as anticoagulation or coronary intervention, and β-blockers may therefore take on a relatively more important role.

Recommendation

Early β-blocker use in the setting of suspected acute MI deserves careful consideration of the relative risks and benefits. Cardiogenic shock appears to be a significant risk, with the potential to outweigh later benefits. These drugs should only be used with frequent hemodynamic assessment and only once the hemodynamic condition after MI has stabilized.

Competing interests

The authors declare no competing interests.

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