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Rationale Behind Practice: Landiolol in Critical Care

A summary of data regarding the use of landiolol as a potential immunomodulator in septic patients and its effectiveness and safety in the management of new-onset postoperative atrial fibrillation (POAF).

Cardiovascular Dysfunction and Sepsis

Cardiovascular dysfunction is a common complication of sepsis. Approximately 40 to 50% of patients with prolonged septic shock develop myocardial dysfunction. The changes induced by sepsis in circulating volume and vessel tone can affect cardiac performance. Another feature of sepsis-induced organ dysfunction is mitochondrial dysfunction which places the cardiomyocytes at risk of adenosine triphosphate depletion. Various mechanisms are at play, including downregulation of beta-adrenergic receptors, depressed post-receptor signalling pathways, impaired calcium liberation from the sarcoplasmic reticulum and impaired electromechanical coupling. All these changes are regulated by cytokines and nitric oxide (NO) (Rudiger and Singer 2007). During sepsis, there is an excessive production of NO, which decreases the sensitivity of the myocardium, which in turn affects the protein kinase and cyclic GMP messenger system (Greer et al. 2015).

There is a high level of inflammation during septic shock that leads to vasodilation and capillary leakage. This decreases cardiac output and can trigger sympathetic activation to ensure the maintenance of vital organ perfusion. The hallmarks of this activation are tachycardia and vasoconstriction. Sepsis guidelines recommend intravascular fluid administration as the first step to manage hypotension, but in patients with sepsis who continue to have an elevated heart rate, there is sympathetic overstimulation which is the result of dysregulation of the autonomic nervous system and the effect of exogenous catecholamines (Unger et al. 2018).

In clinical practice, catecholamines have been routinely used to bring the patient's blood pressure back to normal and help their vital organs recover and function normally. The most used catecholamine is noradrenaline. However, noradrenaline is associated with significant side effects if given at high doses and for extensive periods of time. The drug may increase blood pressure in the short term, but it can damage the body in the long run. That is why the use of catecholamines in patients with sepsis-induced cardiac dysfunction is being questioned (Lall et al. 2021).

New-Onset Atrial Fibrillation Post-Cardiac Surgery

Atrial fibrillation (AF) is one of the most reported arrhythmias after cardiac surgery. The incidence of new-onset post-operative AF (POAF) varies between 30 to 50% after cardiac surgery. The time of onset is typically within 1-5 days after surgery, peaking at day 2. Common risk factors for POAF include advanced age, type and complexity of surgical procedures and patient characteristics. POAF can negatively impact patient outcomes in terms of morbidity, hospital stay, long-term outcomes, thromboembolic stroke, and mortality (Boriani et al. 2019).

As per the 2020 ESC Guidelines for the diagnosis and management of AF, beta-blockers, diltiazem or verapamil are recommended as first-choice drugs to control heart rate in patients with LVEF $\geq 40\%$ and beta-blockers and/or digoxin in patients with LVEF $< 40\%$. In patients with haemodynamic instability or severely depressed LVEF, the guidelines recommend intravenous amiodarone for acute control of heart rate. However, for the first time, landiolol is included in these important

guidelines. Landiolol is described as the only agent with a specific dose recommendation in patients with cardiac dysfunction (dosages of 1 $\mu\text{g}/\text{kg}/\text{min}$ up to 10 $\mu\text{g}/\text{kg}/\text{min}$) (Hindricks et al. 2021).

Landiolol – Fulfilling an Unmet Medical Need

Landiolol is an ultra-short acting, intravenous β_1 -superselective adrenergic receptor antagonist with the highest receptor selectivity of all beta-blockers, a short half-life of four minutes and a low volume of distribution (0.3 l/kg - 0.4 l/kg) (Rapibloc SmPC; Wada et al. 2016). It has a limited effect on blood pressure and inotropy (Shibata et al. 2012) and has a favourable safety profile for patients with renal and hepatic comorbidities (Rapibloc SmPC; Yokoyama 2016). The drug is compatible with pulmonary disorder patients due to its high cardioselectivity (European Heart Journal Supplements 2018) and it has a limited rebound and tolerance effect (Nasrollahi-Shirazi et al. 2016).

The overstimulation of adrenergic receptors can be treated with beta-blockers as these drugs offer attenuation of inflammatory cytokines, improve cardiac function, counteract metabolic dysregulation, prevent negative consequences from sympathetic overstimulation and prevent dobutamine-induced ventricular arrhythmias. Among septic patients with persistent tachycardia, ultrashort-acting beta-blockers such as esmolol and landiolol are associated with reduced 28-day mortality (Hasegawa et al. 2021). Landiolol, compared to esmolol, has a faster onset of action (1 vs 2 minutes) and a shorter half-life (4 vs 9 minutes). This allows rapid titration and an enhanced control of the substance lead-

ing to a better safety profile. In addition, the beta-1 selectivity of landiolol is nearly eight times higher than esmolol (Plosker 2013; Krumpal et al. 2017).

Landiolol has also shown to be effective in treating perioperative tachyarrhythmias and has been reported to be safe in treating patients with heart failure. Post-marketing surveillance studies in Japan illustrated that patients with cardiac dysfunction who received landiolol (continuous infusion, starting at 1 µg/kg/min) for treating AF achieved effective heart rate control without new safety concerns. Landiolol demonstrated to be more effective than digoxin in controlling heart rate in patients with left ventricular dysfunction who had AF. Heart rate control was achieved in 48% of patients treated with landiolol compared with 13.9% with digoxin (Yamashita et al. 2019).

In the J-Land 3S study, significantly more patients with sepsis-related tachyarrhythmia achieved a heart rate of 60-94 beats per minute at 24 hours and a reduced incidence of new-onset arrhythmia than the control group (Kakikhana et al. 2020).

In patients who developed new-onset AF after open-heart surgery (n=134), landiolol achieved a significantly greater success than other treatments in reducing ≥ 20% the ventricular rate. It was concluded that this treatment is effective

in rate control as well as for conversion of postoperative AF and can be used as a safe, first-line treatment for postoperative AF after open-heart surgery and in patients who have undergone off-pump coronary artery bypass grafting (CABG) (Nishi et al. 2013).

Efficacy and safety of landiolol were also compared with amiodarone in the restoration of sinus rhythm for POAF in ICU patients. Landiolol demonstrated a significantly shorter median time required for conversion to sinus rhythm as amiodarone. Adverse events with bradycardia leading to drug discontinuation were observed only in patients receiving amiodarone. Therefore, landiolol could be considered a favourable drug choice over amiodarone for the safe restoration of sinus rhythm in ICU patients with POAF (Shibata et al. 2016).

Conclusion

Controlling the heart rate with landiolol in the ICU often maintains stroke volume. The reduced effects on blood pressure dropping, negative inotropy and the beneficial pharmacokinetic profile of landiolol also decreases the level of complications during treatment. Additionally it is noteworthy to highlight the anti-inflammatory effects of the substance regarding different cytokines, heart tissue damage, and anti-apoptosis effects which can help patients with severe

sepsis to avoid cardiac dysfunction.

Overall, a highly selective beta-blocker like landiolol can be considered a first-line treatment for rate control in patients with AF after cardiac surgery and sepsis. Especially the pharmacokinetic and pharmacodynamic profile makes it a favourable choice in critically ill patients. The substance clearly demonstrated sufficient evidence of reliability with regards to efficacy, safety, and handling in the described clinical settings.

Key Points

- Landiolol, an ultrashort-acting β-blocker, can rapidly control heart rate.
- Controlling the heart rate with landiolol in the ICU can help maintain stroke volume.
- Landiolol has anti-inflammatory effects.
- Landiolol offers effective control of heart rate with minimal impact on blood pressure.
- The safety and effectiveness of landiolol have been successfully assessed in AF with HF.
- The safety of landiolol has been reported to be safe without any major concerns.

Disclaimer

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Summary of Rapibloc® Product Characteristics - current version.

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