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Therapeutic approaches employed in cardiac surgery to manage postoperative atrial fibrillation

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ABSTRACT

Postoperative atrial fibrillation (POAF) is amongst the most common complications following cardiac surgery and often results in prolonged post-surgical hospital stay, stroke, increased mortality and morbidity, and higher medical costs. Many factors are intertwined in the development of this common complication after cardiac surgery such as surgical trauma, left atrial hypertrophy, valvular changes in atrial pressure, pre-existing congestive heart failure, chronic renal failure, or chronic obstructive pulmonary disease (COPD). In addition, POAF is observed to be more common in the elderly, the male gender, and obese patients. Several drugs are known to prevent POAF in cardiac surgery. Despite the great potential that has been done to reduce the incidence of POAF, the incidence of POAF has not changed significantly. In addition, the literature on POAF management is limited. Moreover, although current guidelines advocate antiarrhythmic drugs in the management of POAF after cardiac surgery, they do not completely prevent POAF, so more new interventions should be tested and added to existing known antiarrhythmic drugs. This review aims to compile and compare the most commonly used therapeutic approaches and drugs in the management of POAF, such as beta-blockers, colchicine, amiodarone, onabotulinumtoxinA, atorvastatin, and others, based on their ability to reduce POAF incidence, stroke occurrence and length of hospital stay (LOHS). In addition, we point out the gaps and limitations of clinical research in this area.

Keywords: *Postoperative atrial fibrillation, Cardiac surgery, Stroke, Length of hospital stay size*

1. Introduction

Postoperative atrial fibrillation (POAF) is a serious complication that frequently occurs after heart surgery because it predisposes to more serious complications and increased morbidity and mortality (Rezaei et al., 2020). POAF occurs in 10-65% of patients who undergo heart surgery and frequently begins to appear from the second day after heart surgery (Rezaei et al., 2020; Thein et al., 2018). The severity of POAF mainly depends on secondary events such as stroke, acute kidney injury, heart failure, increased length of hospital stay (LOHS) and prolonged stay in the intensive care unit (ICU) which significantly increases hospital cost (Thein et al., 2018; Waldron et al., 2019; Yadava et al., 2016). Despite great potential done to decrease POAF occurrence, POAF incidence has not changed significantly (Shen et al., 2011; Waldron et al., 2019). In addition, literature for POAF management is limited (Thein et al., 2018). Although current guidelines advocate antiarrhythmic drugs in the management of POAF after cardiac surgery, they do not completely prevent POAF, so more new interventions should be tested and added to existing known antiarrhythmic drugs (Costanzo et al., 2013; Echahidi et al., 2008; Savelieva et al., 2011).

POAF occurs in approximately 35% of patients who have had cardiac surgery and peaks on the second postoperative day (Greenberg et al., 2017). The incidence of POAF among patients who underwent coronary artery

bypass grafting (CABG) surgery ranged from 20% to 30% (Ha et al., 2019). In addition, patients who underwent valve surgery had a higher incidence of POAF ranging from 40% to 60% (Almassi et al., 1997; Ha et al., 2019; Mathew et al., 2004; Pernigo et al., 2017; Villareal et al., 2004). In addition, having POAF increases the risk of developing atrial fibrillation (AF) by five times even one year after heart surgery (Ha et al., 2019; Lee et al., 2014).

The etiology of POAF has not been clearly elucidated or understood, which leads surgeons to test many different types of therapeutic interventions. It includes multifactorial etiology; inflammatory, electrical and metabolic disorders that alter atrial geometry and electrophysiology (Carrascal et al., 2016; Gudbjartsson et al., 2020).

This review aims to compile and compare the most commonly used therapeutic approaches and drugs in the management of POAF, such as beta-blockers, colchicine, amiodarone, onabotulinumtoxinA, atorvastatin, and others, based on their ability to reduce POAF incidence, stroke occurrence and LOHS. In addition, we point out the gaps and limitations of clinical research in this area.

2. Risk factors

2.1. Patient-related risk factors

Elderly patients especially those over 55 years of age have been observed to have a consistent nonlinear relationship with an increased risk of POAF due to structural and electrophysiological abnormalities in the cardiovascular system such as low conduction velocity, elevated atrial fibrosis and loss of myocardial fibers (Costanzo et al., 2013; Gudbjartsson et al., 2020; Reckman & Creemers, 2018; Spach & Dolber, 1986). In addition, there are many other factors related to the patient's history and health status such as previous history of valvular heart disease, AF, coronary artery disease (CAD), cardiomyopathy, hypertension, chronic obstructive pulmonary disease (COPD), preoperative left atrial diameter >4.5 cm and decreased kidney function (Gudbjartsson et al., 2020; Steinberg, 2004). Moreover, hyperglycemia can be a risk factor for POAF in some cardiac surgeries (Reckman & Creemers, 2018). Also, POAF is seen to be more common in Caucasian ethnicity and male gender (Gudbjartsson et al., 2020).

2.2. Operative risk factors

It is essential to maintain a balanced level of electrolytes, especially potassium and magnesium during cardiac surgeries to prevent POAF as hypokalemia and hypo/hypermagnesemia are risk factors for POAF. Furthermore, other factors such as oxidative stress, acute volume overload in the atrium, prolonged ventilator durations and hypoxemia have an impact on the incidence of POAF (Gudbjartsson et al., 2020).

2.2.1. Procedural factors

Some studies have indicated that venous cannulation site, duration of aortic cross-clamp time and duration of cardiopulmonary bypass (CPB) can be risk factors for POAF (Gudbjartsson et al., 2020; Hashemzadeh et al., 2013).

3. Therapeutic approaches

3.1. High efficacy drugs

3.1.1. Beta-blockers

Induction of the sympathetic nervous system has a significant role in the pathophysiology of POAF because it raises intracellular calcium ions, leading to automaticity. This explains the use of beta-blockers in the prevention of POAF (January et al., 2014; Okamura et al., 2019).

Oral beta-blockers

According to Thein, P. M. et al. study, preoperative administration of oral beta-blockers (atenolol, sotalol and metoprolol) showed a 40.4% reduction in the incidence of POAF (Thein et al., 2018). Furthermore, various studies have reported beneficial effects of beta-blockers postoperatively (Nakamura et al., 2020; Sezai et al., 2012; Sezai et al., 2015; Tamura et al., 2017). An increase in bradycardia was observed in the beta-blocker receiving group, which necessitates continuous monitoring of the heart during the hospital stay (Thein et al., 2018) (Table 1).

Table 1: Adverse effects and impact of different therapeutic approaches in the management of POAF

Therapeutic approach	POAF incidence reduction	Stroke incidence	LOHS	Adverse effects
Oral beta-blockers (atenolol, sotalol and metoprolol)	40.4%	No effect	No effect	Bradycardia episodes
Tolvaptan	37.2 %	Was not studied	No effect	kidney function deterioration
Colchicine	33.33%	Was not studied	Decreased by one day	GIT intolerance
Epicardial injection of onabotulinumtoxinA (BoNTA)	23.64 %	Was not studied	No effect	None
Omega 3 (PUFA)	10.68%	Was not studied	Was not studied	None

Transdermal bisoprolol

The dosage form of bisoprolol played an important role in reducing the incidence of POAF preoperatively, as transdermal bisoprolol showed a 46.5% reduction in the incidence of POAF compared to oral bisoprolol (the incidence was 24.5% in the group receiving transdermal bisoprolol and 45.8% in the group receiving oral bisoprolol). However, bisoprolol in both dosage forms did not show any significant effect in decreasing risk of stroke nor LOHS (Table 2). Transdermal bisoprolol showed advantageous outcomes as the transdermal patch showed more steady plasma concentration than oral bisoprolol, inhibiting fluctuations in blood pressure and heart rate accordingly. Furthermore, if hypotension or bradycardia occurs, the transdermal patch can be easily removed while maintaining blood concentration (Okamura et al., 2019). In addition, the rate of absorption of the transdermal patch is lower than that of oral bisoprolol (Drago et al., 2017; Sairaku et al., 2018) which makes it possible to remove the transdermal patch before its maximum blood concentration is reached (Okamura et al., 2019). In the case of gastrointestinal injury and edema associated with cardiopulmonary bypass (Sinclair et al., 1995; Tofukuji et al., 2000) and edema associated with heart failure, gastrointestinal absorption is not possible, so the use of a transdermal patch solves this problem by percutaneous absorption. Besides, transdermal bisoprolol is suitable for patients who are unconscious or have problems swallowing. These findings are based on retrospective studies with a small sample size and a lack of several types of cardiac surgeries that may influence POAF incidence. Thus, future prospective randomized controlled trials are recommended to prove transdermal patch efficacy (Okamura et al., 2019).

Table 2: Efficacy of oral and transdermal dosage forms of bisoprolol in the management of POAF

	Oral bisoprolol	Transdermal bisoprolol
POAF incidence	46%	24%

Beta-blockers versus calcium channel blockers (metoprolol versus amiodarone)

As reported by Kamali et al., metoprolol showed a 70.37% reduction in the incidence of POAF compared to amiodarone. In addition, metoprolol exceeded the efficacy of amiodarone in reducing LOHS in ICU, which was 5.8 days for the metoprolol group and 8.5 days for the amiodarone group (Table 3). The effect of these drugs on stroke was not investigated in this study (Kamali et al., 2017). The limitation of this study was the small sample size.

Table 3: Beta-blockers versus calcium channel blockers (metoprolol versus amiodarone) in the management of POAF

	Amiodarone	Metoprolol
POAF incidence	27%	8%
LOHS	8.5 days	5.8 days

3.1.2. Tolvaptan

Tolvaptan in the early postoperative period showed a 37.2% reduction in the incidence of POAF (Table 1). The effect of tolvaptan on the incidence of stroke or LOHS has not been studied. Furthermore, intravenous beta-blockers were not added with tolvaptan to prevent misleading results but the effect of tolvaptan was observed independently (Nakamura et al., 2020).

Tolvaptan surpass other therapeutic interventions as it overcomes the problem of using high doses of loop diuretics such as furosemide after cardiac surgery; which may be involved in the occurrence of POAF through activation of the renin-angiotensin-aldosterone and sympathetic systems (Gottlieb et al., 2002; Nakamura et al., 2020; Sarraf et al., 2009). Thus, low doses of furosemide may be used postoperatively with tolvaptan because tolvaptan is believed to have the ability to adjust fluid levels and subsequently lower electrolyte levels and maintain patients' hemodynamics. Notably, the doses of furosemide were determined by each physician, which may lead to bias in the treatment of fluid overload. Future prospective studies are needed to investigate the precise postoperative dose and efficacy of tolvaptan in the management of POAF. Also, it is important to ensure that patients are able to take water orally as an increase in urine output and hypovolemia may occur which in turn contributes to POAF (Nakamura et al., 2020).

3.2 Intermediate efficacy drugs

3.2.1 Colchicine

Colchicine showed a 33.33% reduction in the incidence of POAF compared to usual care and a one-day reduction in LOHS but its efficacy in reducing the incidence of stroke has not been studied. Colchicine has not shown any significant adverse events, but severe gastrointestinal manifestations have been observed and may cause therapy termination (Lennerz et al., 2017) (Table 1).

3.3 Low efficacy drugs

3.3.1 Epicardial injection of onabotulinumtoxinA (BoNTA)

Botulinum toxin is a neurotoxic protein made by *Clostridium botulinum* which has anticholinergic activity. Epicardial injection of BoNTA showed a 23.64% reduction in the incidence of POAF without any adverse events. No effect on LOHS has been shown and its effect on stroke incidence has not been studied (Table 1). Future trials with a larger sample size are needed to verify its efficacy, as studies with small sample size weaken the strength of the hypothesis (Waldron et al., 2019).

3.3.2 Omega-3 (polyunsaturated fatty acids) (PUFA)

Omega-3 has been tested in the management of POAF for its anti-inflammatory effect, and several studies have postulated a direct antiarrhythmic activity (Mozaffarian & Wu, 2011; Savelieva et al., 2011). Preoperative use of omega-3 has shown a 10.68% reduction in the incidence of POAF. However, its efficacy in stroke or LOHS has not been reported (Table 1). The efficacy of omega-3 in reducing the incidence of POAF is believed to be more pronounced in cardiac surgeries associated with high-grade inflammation such as open-heart surgeries. Although the sample size was large in the randomized controlled trial included in the Costanzo, S. et al. meta-analysis study, it did not show any beneficial effect of omega-3 in reducing the incidence of POAF (Costanzo et al., 2013).

3.4 Drugs with no efficacy in the management of POAF

3.4.1 Atorvastatin

Atorvastatin showed no significant effect in reducing the incidence of POAF (the incidence was 42.6% in the atorvastatin group and 30.2% in the control group) (Carrascal et al., 2016).

3.5 Non-pharmacological interventions

3.5.1 Atrial overdrive pacing

There are many types of atrial pacing, for example, bi-atrial (BiA) pacing, left-atrial (LA) pacing and right-atrial (RA) pacing. It has been reported that any type of pacing reduces the incidence of POAF compared to no pacing (NP), and BiA pacing has superior efficacy in decreasing the incidence of POAF. However, future studies are needed to investigate the best pacing period, long-term outcomes and relapse of AF. Also, pacing has no effect in reducing the incidence of secondary outcomes such as mortality rate, postoperative bleeding or infection (Ruan et al., 2020).

4. Conclusions and recommendations

Beta-blockers had the highest efficacy in managing POAF, while omega-3 had the lowest efficacy in preventing POAF episodes. Regarding the efficacy of bisoprolol in the management of POAF, changing the dosage form from the oral to the transdermal route showed enhanced efficacy in reducing POAF events. Thus, future studies that should investigate the efficacy of other beta-blockers, in transdermal form, in the management of POAF with various cardiac surgeries are recommended. In addition, atorvastatin has not shown any beneficial effect in the management of POAF or any of its secondary events. Based on our research, there is a clinical research gap in this research area and a lack of knowledge in the current studies, as they do not focus on testing the efficacy of drugs in reducing the incidence of stroke which is a serious complication of POAF. Therefore, further attention and research are needed in future studies on this point. Furthermore, to achieve maximal drug efficacy and enhance patient clinical outcomes, future research should focus on exploring new drug dose forms of the most popularly used medications for the management of POAF.

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