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To determine the Effectiveness of current management for the Prophylaxis of Postoperative Atrial Fibrillation in Cardiac Surgeries

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Postoperative atrial fibrillation is a very common surgical complication encountered in patients undergoing Cardiac Surgery including Coronary Artery Bypass Grafting and Valvular Surgeries, which leads to increase hospital stay and burden on health care providers. The aim of this review study was to to determine the effectiveness of current management for the Prophylaxis of Postoperative Atrial Fibrillation in Cardiac Surgeries and to propose a possible prophylaxis to prevent POAF. 21 research papers were selected and brought under review after carefully considering the current day evidence for prophylaxis and each having its scientific evidence and background. The papers were carefully reviewed and findings were given in favour of Amiodarone, Ascorbate and B-Blockers including Sotalol. This can rightly be concluded from this study that prophylaxis with Ascorbate for 5 days prior to cardiac surgery along with the use of Amiodarone 1.2 g before surgery and 600 mg/day till 3rd post op day and protocol for B-Blockers will significantly reduce POAF. Also POAF is a clinical complication which needs further studies and research to evaluate the effectiveness of the current management for its prevention.

Keywords: Postoperative atrial fibrillation; Cardiac Surgery; Valvular Surgery; CABG

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INTRODUCTION

Post Coronary Surgery the commonest complications is Atrial Fibrillation (AF), occurs in about 25 to 40% of patients [1-4] . Over a period of four decades the rate of AF after Cardiac Surgery has increased by 20% from 10% in the 70's to 30% in the last decade, the rates are much higher for older patients and those undergoing Valvular surgeries [5-6]. Due to the seriousness of the condition and the sensitization of the issue in different forums much attention has now been given to AF as an earnest Arrhythmia. Alot has been said about the prevention of AF and there have been guidelines, trials and meta analyses conducted to come up with an effective strategy for the prevention of postoperative cardiac Atrial Fibrillation (POAF).

This funny rhythm causes prolonged hospital stay after surgery, increased risk for stroke and adds significant cost to the total, hence the economic implications too need addressal. [7,8,9,10,11,12]. A study done in 1996 revealed even in the absence of an eventful clinical problem the AF leads to a prolonged hospital stay of CABG patients by a mean 4.9 days leading to an estimated additional 10000 $ per case [13]. Many approaches including B-Blockers, Amiodarone and Magnesium have been made for the prevention of POAF [14]. Still there is an ever growing need to evaluate the best prophylaxis for the POAF and to audit the current management for Prophylaxis of POAF.

The current study is a review of over 20 medical papers written on the subject to evaluate, audit and make recommendations to come up with a better prophylaxis for POAF.

MATERIALS & METHODS

The medical archives including Pubmed, Embase, index copernicus and index medicus were searched to find out suitable articles already published and written on the relevant subject considering Prevention and prophylaxis of Postoperative Atrial Fibrillation in cardiac surgeries. Different managements for the prophylaxis were found and each had its scientific evidence and background. 20 research papers were selected and brought under review after carefully considering them.

REVIEW: PROPHYLAXIS FOR POST OPERATIVE ATRIAL FIBRILLATION IN CARDIAC SURGERIES

Biatrial Pacing

The most commonly encountered arrhythmia after CABG is AF. [15, 16, 17]. It is very interesting to see that pathogenesis of POAF is perhaps unclear and is taken for multifactorial. There is a whole discussion going on about the electrophysiology of the condition. Due to the local injury that the myocardium gets with the procedure there is development of atrial foci generating electric rhythm.

Biatrial pacing (BAP) is when we activate both the Atriums of the heart at one time. There have been reports that suggest it prevents AF recurrence in paced patients that present with intra-atrial conduction delay (IACD). IACD has a strong association with POAF after CABG. Hence it can be hypothesized that IACD may predispose patients to POAF and BAP may be a an effective tool to prevent it. [18, 19, 20]

There has been evidence showing Prevention of POAF when Biatrial pacing was performed. [21]. A study we took under observation in the current review evaluated the efficacy of biatrial pacing as an effective Prophylactic measure to prevent POAF [22]. Significant reduction in the POAF was with only Four days of BAP after isolated CABG [23]

Atorvastatin

Many trials and researchers have sought to look into the effectiveness of Statins as a prophylaxis for POAF. The first randomized, controlled trial of prophylaxis with statins before elective cardiac surgery was taken up by

ARMYDA (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study group [24, 25]. Special consideration was given to the evaluation of atorvastatin 40 mg/d, started 1 week before surgery, prevents postoperative atrial fibrillation versus placebo. [26]

Another meta analysis concluded significant reduction in POAF and hospital stay with statin therapy prophylactically. [27] Similar results were published by another study which concluded POAF reduction with statin therapy

preoperatively and also proposed the possibility that further research would establish a relation between type and dosage of statin that was used. [28]

N-3 Fatty Acids

Like all other drugs and techniques used for prophylaxis of POAF, the use of N-3 Fatty Acids have also been found to have association in preventing arrhythmias. [29]. The anti inflammatory role of N-3 Fatty Acids is well established and could possibly prevent POAF due to speculation of its Pathophysiology of an anti inflammatory process. [30, 31]. The aim of one such study under consideration was to find out the efficacy of N-3 Fatty Acids in preventing POAF. There was seen a 18.1 % and 54.4 % reduction is Absolute and Relative Risk, respectively in incidence of POAF. [32]

Colchicine

POAF is thought to have a multifactorial etiological development. Imbalance of the autonomic nervous system during surgery, inflammatory process of the Pericardium and fluid shift besides other factors may all contribute leading to POAF. [33]. We know that anti inflammatory therapy can be beneficial in preventing POAF.

A trial, Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) concluded that colchicine was safe and efficacious in the prevention of the PPS and it reduced the risk of developing the syndrome after Cardiac Surgery by 50%. [34]

The study under review reveals that the efficacy and safety index of Colchicine in reducing POAF after Cardiac Surgery was significant. This is an important factor in clinical practise considering the safety and low price of the drug. Also the efficacy of the drug in preventing POAF and Postpericardiotomy Syndrome (PPS), the two most common clinical complications of cardiac surgery, reduces the cost significantly. [34, 35]

N-Acetylcysteine

Recent studies have established that the pathophysiology of POAF may lie in the oxidative stress and inflammation. [36, 37, 38, 39, 40]. Antioxidative agents like Vit C have been attributed to reduction of POAF. [41] Chronic Pulmonary Disease (CPD) is a potential risk factor for POAF [42] The antioxidant nature and mucolytic properties of N-Acetylcysteine (NAC) have demonstrated beneficial effects in CPD. [43]

NAC having significant effect in preventing postoperative respiratory complications, which are risk factors for developing POAF, could be used as a prophylaxis to reduce POAF in patients undergoing Cardiac Surgery, which is evident from the study under review. [44]

Ascorbic Acid

With high risk for stroke and mortality, POAF is an important clinically encountered complication. There is no clear cut answer about the pathophysiology of POAF. it is thought to be multifactorial. Peroxynitrite formation and oxidative stress have been found to have association with formation of POAF. [45] Therefore treatment with ascorbate (antioxidant and peroxynitrite decomposition catalyst) may be helpful along with the use of BAP.

The study under observation found out that Cardiac CABG patients having supplemental Ascorbate for 5 days before surgery had a 16.3% incidence of POAF in comparison to 34.9% in control subjects. [46]

Another similar study audited similar results in favour of reduction in POAF with ascorbate use for patients undergoing CABG. [47]

Amiodarone

A class 3 Antiarrhythmic Drug, Amiodarone is effective in preventing POAF. [48, 49]. Increase myocardial oxygen demand is a side effect we see with the use of B-blockers and negative inotropes. Potassium and magnesium Conc. reduction in the Postoperative Period is key factor leading to the development of inorganic arrhythmias. Identifying and managing this will not put patients to unnecessary use of drugs and their side effects. Magnesium is an important player in keeping a steady Cardiac Rhythm. [50]

Different studies included in the review suggest that patients who underwent Cardiac

Surgery tolerated the preoperative oral use of Amiodarone and significantly reduces rate of POAF, the duration and cost of hospitalization. [51]. Low plasma conc. of magnesium and the patient's old age are all risk factors for POAF. [52]

Another such study presented its findings in favour of Prophylactic use of magnesium sulphate following CABG. Both Amiodarone and Magnesium Sulphate are effective but the initial management should rely on administering magnesium prophylactically. The physician can intervene with amiodarone if prophylactic use of magnesium fails resulting in POAF. [53]

Magnesium Sulphate

Many physiological functions of the body need Magnesium for normal functioning. Hypomagnesaemia may lead to multitude of clinical complications including Muscular trembling, Atrial fibrillation and impaired coagulation etc. these clinical manifestations of hypomagnesaemia are critical to a patient undergoing Cardiac Surgery. [54]

As discussed in the above section, different studies have given their findings in favour of prophylactic use of magnesium, resulting low incidence of POAF and shorter hospital stays. On the other hand studies suggest magnesium sulphate alone might not be sufficient as a prophylactic agent. [55]

Due to conflicting results in previously published Magnesium Sulphate trials, One such study was designed to address methodological shortcomings in the previous studies. The largest randomized, placebo-controlled trial of intravenous (IV) MgSO4 for the prevention of POAF in patients undergoing valvular or CABG surgeries, presented its findings that no marked reduction in POAF occurs with the addition of MgSO4, for patients receiving protocol for B-Blocker. [56]

Similar studies included in our review had results considering prophylactic Mg supplementation as a good preventive measure for POAF. [57]. There was significant reduction in the episodes of POAF in the group receiving Mg. Patients tolerated the drug very well. No side effects were observed. [58].

Sotalol & Beta-blockers

A meta analysis revealed significant reduction in the POAF was seen with the use of Prophylactic B-Blocker and sotalol in Cardiac Surgeries. Though it recommended larger studies need to be conducted to know the cost-effectiveness and efficacy of these drugs. [59]

Another meta analysis pointed out similarities between B-blockers, amiodarone and sotalol in preventing POAF with no significant difference between them. Evidence show prevention of POAF reduces hospital stay but no association was found between reduction of POAF and decrease incidence of stroke. [60] For patients receiving protocol for B-Blocker no marked reduction in POAF occurs with the addition of MgSO4 [56]

RESULTS

Research paper	Drug/technique under review	Study design	Study Sample Size	Result	Inference
Fan K et al [22]	Biatrial Pacing	RCT-4 Groups	132	POAF reduction in BAP group (12.5%) compared with the other 3 groups (LA-36.4%, RA-33.3% & X-41.9%. P≤0.05)	BAP effective, lower cost and SHS.

Levy T et al [23]	Biatrial Pacing	RCT-2 Groups	130	POAF reduction in BAP group (13.8%) compared with (38.5%) X Group. P≤0.001	BAP effective, lower cost and SHS.
Patti G et al [26]	Atorvastatin	RCT-2 Groups	200	POAF reduction in Y Group (35%) compared with (57%) Z Group. P≤0.003	Atorvastatin 40 mg/d 7 days before surgery effective and SHS
Calò L et al [32]	N-3 Fatty Acid	RCT-2 Groups	160	POAF reduction in Y Group (15.2%) compared with (33.3%) X Group. P≤0.013	N-3 Fatty Acid 2g/day 5 days before surgery effective and SHS
Imazio M et al [35]	Colchicine	RDBT-2 Groups	336	POAF reduction in Y Group (12%) compared with (22%) Z Group. P≤0.021	1 mg BD Colchicine 3 days post op effective in preventing AF & PPS , lower cost and SHS.
Ozaydin M et al [44]	N-Acetylcysteine	RDBT-2 Groups	115	POAF reduction in Y Group (5.1) compared with (21.1%) Z Group. P≤0.019	50-150 mg/kg bolus 1 hr before surgery and 40 mg/kg/day for 24 hrs after surgery effective , lower cost and SHS.
Carnes CA et al [46]	Ascorbate	RCT-2 Groups	86	POAF reduction in Y Group (16.3%) compared with (34.9%) X Group. P=0.05	2 gm Supplemental Ascorbate before and 500mg BD for 5 days after CABG attenuates APIPF & reduces

					POAF
Ebade A et al [47]	Ascorbate & $MgSO_4$	RCT-3 Groups	60	POAF reduction in A group (15%) compared with the other 2 groups M-Group (25%) & X Group (40%)	Ascorbate & $MgSO_4$ 2 gm after anesthesia induction and 1g/8h for 5 days after surgery is effective and SHS.
Daoud EG et al [51]	Amiodarone	RDBT-2 Groups	124	POAF reduction in A group (25%) compared with the Z Group (53%). P =0.003	600 mg/day amiodarone seven Days before surgery & 200 mg/day until discharge is effective, lower cost and SHS.
Venzi MMT et al [52]	Amiodarone & $MgSO_4$	RDBT-3 Groups	155	POAF reduction in A group (14%). P=0.14 compared with the other 2 groups M-Group (23%). P=0.82 & Z Group (27%)	72 h IV Infusion of 900 mg/24h Amiodarone, 4g/24h Magnesium & 50ml/24hr Nacl Placebo. Magnesium no effect but Amiodarone is effective after CABG
Tiryakioglu O et al [53]	Amiodarone & $MgSO_4$	RCT-3 Groups	192	Amiodarone significant compared to magnesium sulphate (p = 0.015).	$MgSO_4$ 3g/100ml Nacl over 2h for 12h before surgery till 3rd post op day. Amiodarone 1.2 g before surgery and 600 mg/day till 3rd post op day Nacl Placebo.

Kaplan M et al[55]	$MgSO_4$	RCT-2 Groups	200	AF developed in 15 patients- Group M & 16 patients -Group X. P=0.845	$MgSO_4$ 3g/100ml Nacl over 2h for 12h before, during surgery till 3rd post op day, alone is not sufficient for preventing POAF
Cook RC et al[56]	$MgSO_4$ & B-Blocker	RDBT-2 Groups	677	AF developed in 26.4% patients- Group M & 24.3% patients -Group Z.	IV $MgSO_4$ addition to protocol for B-Blocker didn't reduce POAF
Dabrowski W et al [57]	$MgSO_4$	RCT-6 Groups	120	ECC resulted in a decrease in Mgt. 3.33 mg/min $MgSO_4$ little effect to reduce POAF. 10 mg/min $MgSO_4$ reduced POAF significantly	$MgSO_4$ had little significance to reduce or prevent POAF
Fanning WJ et al [58]	$MgSO_4$	RDBT-2 Groups	99	PSMGS Conc. same (1.90 mEq/L) in group Y & Z. MPSMCI levels were elevated. $P < 0.001$. MPSMCP levels declined. $P < 0.001$. MSGC was high in Group Y than Group Z. $P < 0.001$	Prophylaxis with $MgSO_4$ seem to lessen incidence & severity of POAF after CABG
Burgess DC et al [59]	B-Blocker, Sotalol, Amiodarone, Atrial Pacing & $MgSO_4$	Meta analysis	94 trials	Odds Ratio for all five is B-Blockers=0.69, Sotalol=0.34, Amiodarone=0.48, $MgSO_4$=0.57 & Biatrial Pacing=0.60. All five interventions reduced the incidence of AF, though the effect of BBs is less than previously documented	Prophylaxis effective, lower cost and SHS.
Crystal E et al [60]	B-Blocker, Sotalol, Amiodarone & Biatrial	Meta analysis	52 Trials	Odds Ratio for all four is B-	Prophylaxis effective,

	Pacing			Blockers=0.39, Sotalol=0.35, Amiodarone=0.48 & Biatrial Pacing=0.46. B-Blockers, Sotalol, and amiodarone Reduce POAF with no marked difference between them	lower cost and SHS. Data on stroke reduction is incomplete.
Archbold RA et al [61]	$MgSO_4$	Special Review	NA	Hypomagnesaemia may predispose POAF. Serum [Mg] falls due to haemodilution and beta-adrenergic activation after CABG.	$MgSO_4$ had little significance to reduce or prevent POAF
Weber KU et al [62]	Selective versus non-selective antiarrhythmic	RCT-2 Groups	214	Non-selective approach exposed everyone to the possible side-effects of sotalol. Selective approach, reduced POAF 76% to 50%. P=0·0295 compared to a reduction from 44% to 26%. P=0·0065 when everyone treated.	Clinical risk prediction based selective approach is Cost-effective and ensures safety of low-dose sotalol as prophylaxis for POAF after CABG.
Koniari i et al [64]	B-Blocker, Sotalol, Amiodarone & $MgSO_4$	Systematic Review	NA	B-Blocker for all cases of patients undergoing cardiac surgery (until contraindicated). Sotalol for POAF prevention in place of conventional B-Blockers has been advocated (Grade A recommendations). when B-Blocker can not be used Amiodarone can be used as an alternative prophylaxis for POAF or may also be used in conjunction to B-Blocker in high risk cases.	Prophylaxis effective, lower cost and SHS.

Wang HS [65]	Carvedilol	Meta analysis	6 trials-765 subjects	Reduction in POAF 0.37 to 0.64. P=0.001 was seen with Carvedilol and it is Better than metoprolol for prevention of POAF 0.37 to 0.70. P=0.001	Carvedilol is effective & superior to metoprolol for prophylaxis of POAF

SHS-Shortened Hospital Stay

RCT-Randomized Clinical Control Trial

BAP-Biatrial Pacing

LA-Left Atrial Pacing

RA- Right atrial pacing

RDBT-Randomized Double Blinded Trial

PPS-Postpericardiotomy Syndrome

APIPF-Atrial Pacing-Induced Peroxynitrite Formation

X-Control Group

Y-Intervention Group

Z-Placebo Group

A-Amiodarone Group

M- $MgSO_4$ Group

ECC-Extracorporeal Circulation

Mgt- Total Magnesium Conc.

PSMGS-Preoperative Mean serum Magnesium Concentration

MPSMCI-mean postoperative serum magnesium concentration in Intervention Group

MPSMCP-mean postoperative serum magnesium concentration in Placebo Group

MSGC-mean serum magnesium concentration

DISCUSSION

A study done to evaluate the effectiveness of Biatrial Pacing presented its finding in favour of Biatrial Pacing than single site atrial pacing. The paper also concluded that carefully identifying 'at risk' population for developing POAF and the use of intense prophylactic therapy would lead to shorter hospital stay and decrease the overall cost [22]. Another paper pointed out similar findings and postulated reduced postoperative complications after CABG with the use of BAP [23]

Use of statins has been advocated in various studies as a prophylaxis for POAF. Strong association was found resulting in reduction of POAF with the use of 40 mg/d atorvastatin (started 7 days preoperatively for elective Cardiac Surgery) [26]

Evidence can be found on the use of N-3 Fatty Acid for prevention of POFA. A substantial reduction in POAF (54.4%) associated with consequent shorter hospital stay was demonstrated in patients having CABG. [32]

NAC being a glutathione precursor is basically an antioxidant. Major findings of one the studies included in the review on NAC were lower incidence rates of POAF in intervention group in comparison to Placebo group. [44]. This study also supports the idea of the relation between POAF and Oxidative stress.

One of the study included in the review was important in reaching a conclusion because it had significant amount of patients (57%) included in the study who underwent Valvular surgeries besides those undergoing CABG only. A 7 day oral prophylactic use of Amiodarone before an elective

Cardiac Surgery had reduced POAF by 50%, consequently reducing burden on the health facility, lower the total cost and duration of hospital stay and most importantly fewer postoperative clinical complications. No evidence of intra or postoperative complications was found with the use of Amiodarone. The heterogeneity of the study population highlights how efficient is the drug for both CABG and Valvular surgery [51]

POAF after Cardiac and Valvular surgeries is a nuisance which leads to a number of medical complications and increase hospital stay. Preventing such an event from occurring would not only benefit the patient vis a vis health but also decrease hospital burden. Low levels of magnesium have been attributed to POAF but the sole correction or management of magnesium would not prevent POAF. [54]

A study (27 trials) included in our review evaluated 3840 patients for POAF with B-Blocker. There was 14% reduction of POAF in the intervention group (19%) in comparison to control group (33%) [60]. The same study evaluated 1294 patients for POAF with sotalol. There was 20% reduction of POAF in the intervention group (17%) in comparison to control group (37%). It also evaluated 1384 patients for POAF with amiodarone. There was 14.5% reduction of POAF in the intervention group (22.5%) in comparison to control group (37%). Comparison of Sotalol to conventional B-Blocker included 900 patients. There was 10% reduction of POAF in the Sotalol group (22%) in comparison to other B-Blocker group (12%). [60]

Another study in our review concluded its recommendations in favour of B-Blocker for all cases of patients undergoing cardiac surgery (until contraindicated). The use of sotalol for POAF prevention in place of conventional B-Blockers has been advocated (Grade A recommendations) [63]. In cases where B-Blocker can not be used Amiodarone can be used as an alternative prophylaxis for POAF or may also be used in conjunction to B-Blocker in high risk cases. [64]

Another study included in the review concluded that carvedilol is superior to metoprolol in preventing POAF for patients undergoing cardiac surgery. [65]

Another important perspective here is the use of Cardiopulmonary pump. A study shows marked decrease in the AF after off pump surgery in comparison to conventional CABG [66] which makes us to think about systemic inflammatory reaction with the use of Pump may be a key in understanding POAF [67, 68, 69]. In one of the study a significant association was found between the 174C/G polymorphism of the promoter of Interleukin-6 gene and postoperative Interleukin-6 levels leading to AF Development [70]

CONCLUSION

Postoperative atrial fibrillation is a very common surgical complication encountered in patients undergoing Cardiac Surgery including Coronary Artery Bypass Grafting and Valvular Surgeries, which leads to increase hospital stay and burden on health care providers. The papers were carefully reviewed and findings were given in favour of Amiodarone, Ascorbate and B-Blockers including Sotalol. This can rightly be concluded from this study that prophylaxis with Ascorbate for 5 days prior to cardiac surgery along with the use of Amiodarone 1.2 g before surgery and 600 mg/day till 3rd post op day and protocol for B-Blockers will significantly reduce POAF. Also POAF is a clinical complication which needs further studies and research to evaluate the effectiveness of the current management for its prevention.

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