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Can Hypoxia Induced Pulmonary Hypertension be Treated with a Combination of $MgSO_4$, Alpha Blocker as Well as Angiotensin Converting Enzyme Inhibitor?

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Abstract

Pulmonary hypertension (PHT) has classically been treated with expensive vasodilators. Through the treatment of hypoxia-induced PHT as well as postoperative hypoxia by proxy PHT, possible alternatives in treatment have been discovered. Results of the aforementioned treatments and patient interventions have been discussed in this paper. Medications discussed individually are $MgSO_4$, ACE inhibitors, and alpha blockers as well as their implementation in therapeutic regimens. The conclusions drawn from those largely successful interventions lead to a proposal for the development of an alternative medication for the hypoxia-induced pulmonary hypertension that theoretically would prove to be as inexpensive as it would be effective. Bringing together the results of the aforementioned research, this medication would consist of $MgSO_4$, ACE Inhibitors, and alpha blockers. It is inferred that a triple therapy of the three drugs would allow for synergistic effects and reduce the side effects to a minimum. The goal would be to develop a medication that can be used for all the communities where it is needed, regardless of their medical development or financial flexibility.

Keywords: ACE-I, Alpha adrenoceptor blocker, High altitude pulmonary hypertension, Hypoxia induced pulmonary hypertension, $MgSO_4$

1. Context

Pulmonary hypertension (PHT) is a complex disorder, in which multiple factors can contribute either simultaneously or individually to its etiology. Hypoxia may be a root cause for pulmonary hypertension, so treatments should aim to treat hypoxia directly or indirectly. Hypoxia can be triggered by many factors, all of which have led to specific treatments being developed to target those factors individually. The mechanisms of these factors were studied and used to develop conclusions about a potential combination of medications using the effects of each individual treatment to gain synergistic benefits and reduce their side effects. Given the individual factors that can lead to hypoxia-induced PHT, and the common attributes of the respective treatments could be lead to suggest the combination of the drugs.

This report aims to suggest the combination of widely available and affordable MgSO4 as well as alpha blockers / Angiotensin Converting Enzyme Inhibitor (ACE-I) could be used to treat hypoxia-induced pulmonary hypertension (HIPH). All of these medications have been shown to be safe, efficacious and efficient in treating different conditions. Since these are acceptable and most importantly affordable medications, it is proposed that they are used as viable alternatives to the existing anti-pulmonary hypertensive drugs.

1.1. Current medications used to treat high altitude PHT

Different authors have described the successful use of sildenafil for treating some of the effects of HIPH.

Endothelin antagonists are effective for the treatment of PHT at low altitude and attenuate altitude-induced pulmonary hypertension in normal subjects (1). However, there are no data on their potential usefulness in terms of the prevention or treatment of exaggerated pulmonary hypertension (1).

For prevention and treatment of exaggerated PHT during acute high altitude exposure, calcium antagonists remain a cheap, effective, and well-documented choice (2).

2. Reduced partial pressure of oxygen leading to Hypoxia-Induced Pulmonary Hypertension (HIPH)

Reduced partial pressure of oxygen is one of the major factors causing HIPH. This is most prominent in those living at high altitudes, since decrease in oxygen levels occurs naturally at higher altitudes. Whilst different medications have been used to treat these conditions, such as those used by patients suffering from high altitude pulmonary hypertension (HAPH), they have proven not to be globally accessible (1). Existing vasodilators are generally unaffordable for many people and health care systems; therefore, it is required to provide a solution in this regard.

The mechanisms behind pulmonary vasoconstriction are related to the bioavailability of calcium. Calcium-channel blockers have commonly been administered to counter the effects of calcium at target sites. By blocking calcium channels, pulmonary

vasoconstriction can be induced using natural biological mechanisms(2).Similar effects could be seen in magnesium as a naturally existing calcium antagonist. It is a muscle relaxant, vasodilator, sedative, and antithrombotic agent. We could take advantage of the mentioned same mechanisms to treat PHT.

2.1 Magnesium sulfate as a treatment for Hypoxia-Induced Pulmonary Hypertension (HIPH)

Abu-Osba et al. (1990) demonstrated that a sharp increase in the mean pulmonary artery pressure occurred in anaesthetized sheep when breathing 10% oxygen. During hypoxia, this pressure fell quickly to baseline after $MgSO_4$ infusion(3).

The study demonstrated conclusively that $MgSO_4$ decreased pulmonary artery pressure in sheep during HIPH without affecting blood pressure and cardiac output negatively.

Systolic pulmonary arterial blood pressure (SPAP), diastolic arterial blood pressure and mean pulmonary artery pressure (MPAP) were increased significantly during hypoxia compared with hyperoxia ($p<0.001$), with no change after administration of a placebo. SPAP and MPAP were decreased ($p<0.01$, <0.001 respectively) following infusion of $MgSO_4$, whilst systemic mean BP and SBP were not changed ($p<0.1$ and <0.1). Cardiac output was not changed following Mg infusion ($p<0.6$) and heart rate was decreased transiently ($p<0.001$) (3).

In this study it was concluded that $MgSO_4$ decreases pulmonary artery pressure significantly during HIPH, without affecting the systemic blood pressure and cardiac output.

Cropp et al. 1968 had shown similar results in canines. An increase in serum magnesium to 5-6 mmol/l was shown to block hypoxic pulmonary vasoconstriction without causing deleterious changes in haemodynamics or pulmonary ventilation (4).Using this knowledge, Abu Osba et al. 1995,successfully introduced $MgSO_4$ in the treatment of persistent pulmonary hypertension in the neonates (5). Numerous clinical studies confirmed the beneficial action of this drug on neonates with persistent pulmonary hypertension (6). Patole SK and Finer NN in 1995 concluded that:"there appears to be sufficient evidence at present to justify a prospective randomized controlled trial to evaluate the role of magnesium infusion as a specific pulmonary vasodilator for the treatment of pulmonary hypertension in hypoxic human newborns"(7).

2.2 Side effects

Despite the evidence that $MgSO_4$ has positive effects on reducing HIPH (at least in neonates, sheep and dogs), there has been no further research evaluating its mechanism. This may be attributed to the fact the $MgSO_4$ is not patented (and cannot be patented), or that nitric oxide (NO), sildenafil and bosentan were introduced and marketed as the drugs of choice in treating PHT.

It is noteworthy that whilst magnesium antagonizes the entry of calcium ion into smooth muscle cells, it promotes vasodilatation that is non-specific. Whilst potentially lowering the pulmonary vascular resistance, it causes a fall in systemic blood pressure in neonatal models of hypoxic or septic pulmonary hypertension. This should be borne in mind as a potential side effect of Mg administration, but is not an encompassing reason to halt further studies.

3. Pulmonary valve stenosis and alpha adrenoceptors and their relations withPHT

Previous research showed that patients with pulmonary valve stenosis have elevated alpha blocker in their circulating cells dropping to normal values ten minutes after balloon dilation (8). Additionally, patients with cyanotic congenital heart disease demonstrated elevated alpha receptors when compared to those with normal oxygen saturation (9,10). In fact, oxygen saturation negatively correlated with alpha receptors; the lower the oxygen saturation is, the higher the alpha receptors will be.

These observations were utilized to treat neonates with critical pulmonary valve stenosis, who remained hypoxic despite successful balloon dilation (11). Our assumption was that alpha receptors remained high in these neonates precisely due to the associated hypoxia. When an alpha blocker was added to their therapeutic regimen, the hypoxia was improved in most patients within hours. On other occasions, ACE inhibitors were also used to treat cyanosis in these patients successfully(12,13).

3.1 Alpha-adrenoceptors in circulating cells correlate with balloon dilation of pulmonary valve stenosis

We conducted a study to measure the density and activity of beta and alpha- adrenoceptors in circulating cells before and 10 minutes after balloon dilation of pulmonary valve stenosis. The hypothesis was that beta-adrenoceptors would rise after the procedure due to the stress of the procedure itself, whilst alpha-adrenoceptors would remain unchanged. Measuring adrenoceptors on the circulating cells comes from the assumption that beta and alpha receptors on the circulating cells might represent a distribution of density and effectiveness of these receptors on cardiac, systemic and pulmonary vascular myocytes. A total of 31 patients with pulmonary valve stenosis were included in the study. As a control group, we examined the adrenoceptor activities in 15 patients with small patent ductus arteriosus (PDA) undergoing transcatheter closure of their PDA. As expected, the beta- receptors were within normal

ranges before balloon valvuloplasty but after the procedure they were doubled in range while increasing the epinephrine levels. Surprisingly, the alpha receptors on the platelets were found to be significantly elevated in pulmonary valve stenosis before the intervention; however, they dropped to normal values 10 minutes after the procedure (8).

When looking at the adrenoceptors in other categories of congenital heart diseases, we noticed that there was a difference in the behavior of alpha receptors in tetralogy of Fallot between the patients with low oxygen saturation comparing to those with normal oxygen saturation. Alpha adrenoceptors were elevated in patients with low oxygen saturation. In fact, alpha- adrenoceptor activity was elevated by 81% ($p<0.05$) in cyanotic children (compared with the control group of PDA). Additionally, there was a negative correlation between alpha adrenoceptor density and oxygen saturation; and the regression coefficient was -0.6 (9,10).Given that there is a direct (negative) relation between alpha adrenoceptor density and oxygen saturation; the lower the oxygen saturation is, the higher the alpha receptor density will be (9,10).

3.2 Treatment as a result of alpha-receptor related findings

For some time, we did not know how to use these findings (namely elevated alpha- receptors in patients with pulmonary valve stenosis and with hypoxia). A few years later, two neonates with critical pulmonary valve stenosis did not improve their oxygen saturation and were in critical condition in spite of successful balloon dilatation. It was hypothesized that alpha-receptors were not decreased in these neonates after the intervention, possibly due to the associated desaturation (11). In these particular patients, the desaturation could be explained by the reduced compliance of the right ventricle due to excessive hypertrophy. Increased sympathetic activity in pulmonary vasculature may result in pulmonary vasoconstriction and resistance. Such an increase in the right ventricular muscle thickness can reduce its compliance. Both factors can potentially reduce antegrade flow into the pulmonary circulation and increase right to left shunting across the atrial septal defect and hence cause oxygen desaturation.

Based on these assumptions, phentolamine, an alpha blocker, was used successfully for the two neonates. Phentolamine improved the clinical status dramatically; the patients could be extubated within a few days and could be discharged into home (11). In another case, phentolamine was found to be successful in the subacute management of a neonate with critical pulmonary valve stenosis. The patient remained prostaglandin and oxygen dependent for 2 weeks following successful valvuloplasty and responded almost immediately to phentolamine infusion. Before discontinuing IV phentolamine, oral angiotensin converting enzyme inhibitor was administered with the idea that this medication might have a similar effect on pulmonary vasculature and right ventricular compliance to that of phentolamine, albeit through different mechanisms of action (12).

A case series that was published in 2015 in 20 patients showed the success of the aforementioned therapeutic regimen (14).

4. Theoretical background behind using ACE I

Angiotensin II leads to vasoconstriction of peripheral systemic pulmonary vasculature. ACE-I blocks conversion of angiotensin I to angiotensin II. By doing this, it lowers arteriolar resistance, increases venous capacity, and lowers resistance in the pulmonary vasculature. ACE-I increases bradykinin [agonist of nitric oxide synthase (NOS)], leading to increase in nitric oxide (NO), thus encouraging further vasodilation of the pulmonary vasculature. It facilitates forward flow into the lungs, whilst reducing the afterload. Vasodilation is thus allowed to occur, cardiac output is increased, and perfusion and overall oxygenation will be improved. Nitric oxide modulates cardiac function by abbreviating the systolic contraction, thus enhancing diastolic relaxation (15). A combination of blocking alpha-2 adrenoceptors and ACE-I improves compliance of the right ventricle leading to the improvement of RV inflow, decrease in right-to-left shunt at atrial level and increase in the RV stroke volume.

5. Conclusions about the efficacy of combiningmedications

Our hypothesis in combining all three drugs is contingent on the following: As each aforementioned medication has been successfully used to treat either hypoxia or hypoxia induced pulmonary hypertension, synergistic effects should be gained by combination of the three drugs. If hypoxia, because of low oxygen-partial pressure, induces PHT in people living at high altitudes, using $MgSO_4$, the combination of alpha blocker and ACE-I could be an effective, safe, and affordable way to treat these patients. The hypothesized synergistic effect might allow to give smaller doses than normally recommended, leading to reduce potential side effects. The three medications are already in use for different illnesses and are proven to be safe. Furthermore, they are prevalent and affordable, especially for underdeveloped countries.

6. Goals of future studies and medical trials

The aim of our intervention is to introduce the combination of $MgSO_4$, alpha blocker and ACE-I in management of the aforementioned cases.

The first potential candidates will be the neonates born at high altitude and showing poor adaptation to

their hostile environment and manifesting with severe hypoxia.

The second proposal is a randomized double-blind study. The proposed combination would be administered to high altitude climbers suffering from symptoms of altitude sickness. The group in question would receive either a placebo or the suggested combination of drugs.

The third project considers to give this treatment to the people who are suffering from symptoms of PHT at high altitude, given that the safety of these medications has been already well established.

These drugs could be used as a universal solution for those including children and adults suffering from PHT, across a wide spectrum of communities. The possibility of an affordable and easily available solution cannot be denied. Further studies are the responsibility of all those concerned with the wellbeing of these patients.

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Conflicts of interest

No conflicts of interest.

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