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Comparison of the additive effects of intravenous methyl prednisolone with that of intravenous pentoxyfylline on low tidal volume normal frequency ventilation as a lung protection strategy during cardiopulmonary bypass that improves immediate postoperative outcome

Abstract

Background: Reperfusion injury and inflammatory mediators introduced by cardiopulmonary bypass (CPB) increase postoperative lung dysfunction. In this study efficacy of Pentoxyfylline or methylprednisolone along with low volume ventilation on cardiopulmonary bypass-induced postoperative lung dysfunction was evaluated.

Methods: Sixty three (n=21) adult patients, undergoing elective valve replacement surgery received either methyl prednisolone (Group M) or Pentoxifylline (Group P) along with low volume ventilation or only low volume normal frequency ventilation (Group V) during CPB. Ventilation was continued with 100% oxygen during CPB with tidal volume of 2ml/kg body weight in all groups.

Results: Inspiratory capacity were significantly higher in both Group M (2333.33±241.52) and Group P (2404.76±201.18) than in Group V (1666.66±577.35) (p=0.00 and p-=0.00 respectively) after extubation. It was significantly lower in Group V (2333.33±912.87) than Group M (2833.33±241.52) (p=0.013) and Group P (2952.38±150.39) (p=0.002) also on Day 2 after extubation. Extubation was significantly earlier in Group P (8.55±0.46) than Group V (18.857±27.49) (p=0.001). It was earlier in Group M (12.66 ±5.91) than Group V but that was not significant statistically (p=0.07). ICU stay was significantly shorter in Group M (1.3±0.3) and Group P (1.44±0.18) than in Group V (2.0±0.00) (p=0.00 and p=0.00).

Conclusion: Anti-inflammatory agents like methylprednisolone or Pentoxyfylline along with low volume normal frequency ventilation should be considered as lung protection strategies during CPB.

Keywords: pentoxyfylline, methylprednisolone, cpb, lung protection, significantly, ventilation

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Abbreviations: CPB, cardiopulmonary bypass; IL, interleukin; PTX, pentoxyfylline; CPAP, continuous positive airway pressure; ACC, aortic cross clamp

Introduction

Postoperative pulmonary dysfunction is a common complication after cardiopulmonary bypass (CPB).[1] Though there has been lots of improvement in the fields of surgery, perfusion and anesthesia in both skill and technologies during previous years, postoperative pulmonary complications cannot be avoided completely.[2] The ultimate outcome for all types of pulmonary complication is hypoxemia with its variations;[3] incidence of adult respiratory distress syndrome is 2% while incidence of atelectasis is 64% after CPB.[4,5] Postoperative lung dysfunction may even persist for weeks after cardiac surgery.[6] The fast-track extubation, is becoming popular increasingly nowadays, so, prolonged postoperative ventilation is considered as increased morbidity.[7] The contributory factors of pulmonary complication, causing "post perfusion lung syndrome" are intravascular micro aggregates,[8] leukocyte activation;[9] interstitial lung edema,[10] lung tissue hypoxia,[11] and alterations in surfactant activity.[12] Alveolar collapse or atelectasis is an important cause of postoperative respiratory dysfunction.[1] It causes large shunts along with impaired oxygenation of blood.[13] Cardiopulmonary bypass (CPB) produces an inflammatory response due to interaction of blood with an extra corporeal circuit. The lungs are also affected by this inflammatory response.

Proinflammatory mediators and cytokines including interleukin (IL)-1, IL-2, IL-6, IL-8, and tumor necrosis factor-α produced during CPB cause polymorphonuclear neutrophil activation.[14,15] and thereby cause lung injury. To reduce CPB induced organ damage, drugs like hydrocortisone, dexamethasone, methyl prednisolone, protease inhibitor like aprotinin and free radical scavengers, have been tried.[16] Corticosteroid administered before CPB, reduce the release of proinflammatory mediators such as IL-6, IL-8, and tumor necrosis factor-α.[17] Pentoxyfylline (PTX) is amethylxanthine derivative and a phosphor diesterase inhibitor, inhibits leukocyte activation, minimize lung injury produced by activated leucocytes.[18] It also

inhibits *in vitro* neutrophil activation, adhesion, chemotaxis, and oxidant release, inflammatory action of IL-1 and TNF on neutrophil function.[19] Hoffman et al.[20] found patients receiving Pentoxyfylline had significant shorter duration of mechanical ventilation, decreased need for haemo filtration, and a shorter intensive care unit stay after CPB. Inaba et al.[21] found that glucocorticoid minimized intraoperative increment of plasma endotoxin and IL-6 levels after CPB. Their study didn't measure the postoperative pulmonary function outcome. Several ventilation strategies were evaluated by different authors to limit pulmonary dysfunction after CPB which from CPAP (continuous positive airway pressure) to low volume high frequency ventilation. Zabeeda et al.[22] observed higher PaO2 and lower P(A-a)O2, 5minutes after weaning from CPB with CPAP than their counterparts who received low frequency, high volume ventilation in CABG patients. Massoudy et al.[23] found small improvement in PaO2/FiO2 ratio in the ventilated group during CPB. No study could be found in literature review till date that have combined the beneficial effects of anti-inflammatory therapy with low tidal volume normal frequency ventilation to evaluate the pulmonary function outcome after cardiopulmonary bypass. This study compare the additive effects of intravenous methyl prednisolone with that of intravenous Pentoxyfylline, if any, on low tidal volume ventilation as a lung protection strategy during cardiopulmonary bypass to improve immediate postoperative outcome.

Materials and methods

It was a prospective, randomized, double blinded, placebo controlled study. After obtaining approval of the Institution Ethics Committee and informed written consent from patients, sixty three patients of age group 18 years to 65 years of either sex, posted for elective valve replacement surgery under cardiopulmonary bypass (CPB) were included in the study. Patients with pregnancy, uncontrolled heart failure, serum creatinine level > 2mg/dl, any concomitant systemic disease, history of allergy to any of the study drugs and smokers were excluded from the study. The patients were randomly assigned to any of the three groups by a computer generated randomization chart. Once the patients were wheeled inside the operation theatre, 5 lead E.C.G and pulse oximeterprobe were attached and monitoring was commenced. Then under local anesthesia an intravenous line was inserted in the right dorsum while arterial line was inserted in the left radial artery and arterial blood pressure monitoring was started. Induction of anesthesia was done with injection fentanyl 5µg/kg and sleep dose of injection thiopentone sodium. Intubation of trachea was facilitated with injection rocuronium bromide 1.0mg/kg. The central venous cannula was inserted in the right internal jugular vein. Group P patients [n=21] received intravenous Pentoxyfylline (300-mg dissolved in 100ml of normal saline) and group M patients [n=21] received intravenous methyl prednisolone (30mg/kg dissolved in 100ml of normal saline) while group V patients [n=21] received same volume of normal saline (100ml) over 20minutes immediately after induction of general anesthesia prior to initiation of cardiopulmonary bypass. The intravenous infusion was prepared by an anesthesia resident and data in the ICU was collected by a surgery resident and they were not involved in the study. Before surgical incision, all patients received inj fentanyl 2µg/kg and inj midazolam 0.02mg/kg. Inj fentanyl was repeated as 2µg/kg before sternotomy.

Anaesthesia was maintained with inj fentanyl, midazolam, vecuronium, and isoflurane and nitrous oxide in oxygen (till onset of CPB). Nitrous oxide was discontinued 5 minutes before onset of CPB. All patients received inj heparin 4mg/kg before CPB and activated clotting time (ACT) was maintained >480seconds. After onset of CPB and cross clamping of aorta ventilation was continued in all patients with one fifth of the previous tidal volume while the respiratory rate was continued as before. In all three groups normal ventilation was restored after release of aortic cross clamp. Surgeons were asked to inform any disturbance in the surgical field due to ventilation during CPB so that ventilation may be stopped.

Comparison between the three groups was done with respect to the following outcome parameters.

1) Evaluation of PaO2 and PaCO2 after intubation, just after commencement of CPB, after removal of aortic cross clamp and after weaning off CPB
2) Duration of postoperative ventilation,
3) Duration of ICU stay
4) Duration of Hospital stay
5) Inspiratory Capacity--after extubation (Day-1) and 24 hrs. After extubation (Day-2).

Statistical analysis

For the purpose of sample size calculation, extubation time was taken as the primary outcome criteria. It was calculated that 21 subjects would be recruited per group in order to detect a difference of 3hours in extubation time between any two individual groups with 80percent power and 5percent probability of type I error. This calculation assumed a standard deviation of 6hours in the outcome parameter giving a root mean square standardized effect value of 0.5 for the three groups. Data were summarized by descriptive statistics. Numerical variables between groups was compared by ANOVA (analysis of variance) followed by Tukey's post-hoctest in order to detect differences between two individual groups, if ANOVA returned a p value<0.05. If variables are non-parametric then Kruskal-Wallis test was used instead of ANOVA and Tukey's test. A categorical variable was compared between groups by Chi-square's test or Fisher's exact test as appropriate. All analyses were two tailed and p<0.05 was considered statistically significant. Statistical method used was SPSS Statistics version 17 ·Illinois, Chicago: SPSS Inc., 2008

Results

Types of surgery in three groups have been depicted in (Table 1). After analyzing the data of 63 patients, 21 patients each in three groups, it was found that three groups were similar regarding age, body wt, sex, duration of aortic cross clamp (ACC) and CPB (Table 2). The pCO2 level were similar in three groups after intubation (Group P 30.37±0.62, Group M 32.05±3.98, Group V 38.85±6.90), during CPB (Group P 29.92±0.76, Group M 32.33 ±2.79, Group V 35.19±6.07), after release of ACC (Group P 33.17±15.56 , Group M 30.07±2.39, Group V 31.52 ±5.43) and after weaning off CPB (Group P 29.52±0.79, Group M 27.89±2.20, Group V 32.72±6.45) (Graph 1,2). The pO2 level was lower in Group P than the other two groups during CPB (Group P 346.01 ±148.20, Group M 510.91 ±99.48, Group V 483.71±137.70), after release of ACC (Group P 378.65±85.18, Group M 515.86 ±123.30, Group V 448.28±169.79) and after weaning off CPB (Group P 346.57±52.03, Group M 537.41±55.33, Group V 441.60±99.43) as illustrated in (Figure 1). Inspiratory capacity were significantly higher in both Group M (2333.33±241.52) and Group P (2404.76±201.18) than in Group V (1666.66±577.35) (p=0.00 and p-=0.00) respectively after extubation as illustrated in (Figure 2 & 3).

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It was significantly lower in Group V (2333.33±912.87) than Group M (2833.33±241.52) (p=0.013) and Group P (2952.38±150.39) (p=0.002) even on Day 2. Extubation was significantly earlier in Group P (8.55±0.46) than Group V (18.857±27.49) (p=0.001). It was earlier in Group M (12.66±5.91) than Group V but that was not significant statistically (p= 0.07). ICU stay was significantly shorter in Group M (1.3±0.3) and Group P (1.44±0.18) than in Group V (2.0±0.00) (p=0.00 and p=0.00). Group M (6.21±0.4) and Group P (6.0±0.0) patients were discharged significantly earlier than patients of Group V (7.14±0.35) from the hospital (p =0.00 and p=0.00). There were no significant difference between the Group M and Group P regarding extubation, ICU stay and discharge from hospital (Table 3).

Table 1 Types of Surgery [Group V, ventilation group; Group M, methyl prednisolone group; Group P, pentoxifylline group]

	Ventricular Septal Defect	Aortic Valve Replacement	Atrial Septal Defect	Mitral Valve Replacement	Single Atrium	Double Valve Replacement	Ruptured Sinus of Valsalva	Tetralogy of Fallot	Open Mitral Commissurotomy	Total
Group V	2	2	2	8	1	3	1	1	1	21
Group M	1	3	4	11	0	1	1	0	0	21
Group P	2	4	2	12	0	0	1	0	0	21

Table 2 Demographic profile along with Aortic Cross Clamp time (Axcl) and duration of CPB (CPB) [Group V, ventilation group; Group M, methyl prednisolone group; Group P, pentoxifylline group]

	Group V	Group M	Group P	P value
Age (year)	29.83±10.45	35.66±9.52	35.0±11.95	N.S
Body Wt (Kg)	43.72±11.06	51.09±13	54.00±9.15	N.S
Sex (M:F)	10:11	11:10	10:11	N.S
Axcl Time (min)	60.66±28.03	61.04±22.72	51.95±17.17	N.S
CPB Time (min)	84.33±41.95	81.09±22.81	88.76±16.81	N.S

Table 3 Comparison between three groups regarding extubation, ICU stay and discharge

	Gr V	Gr M	Gr P	p between	p between Gr V vs Gr MP	p between Gr P vs Gr M
Extubation (hrs)	12.6±5.9	8.8±4.3	8.5±0.4	0.07	0.001	N.S
ICU Stay (Days)	2±0	1.3±0.3	1.4± 0.1	0	0	N.S
Hospital Stay (days)	7.1±0.3	6.3±0.4	6.0± 0.0	0	0	N.S

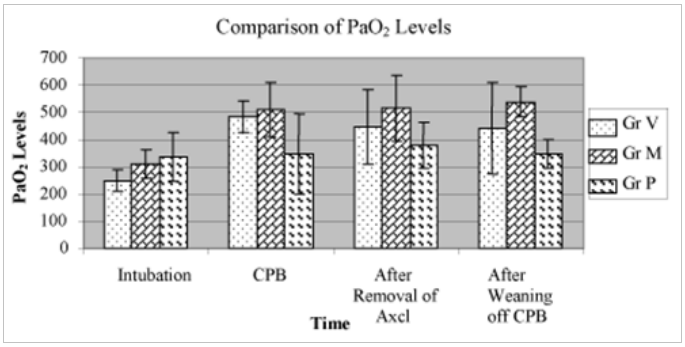

Figure 1 Comparison of PaO2 levels in three groups [Group V, ventilation group; Group M, methyl prednisolone group; Group P, pentoxifylline group].

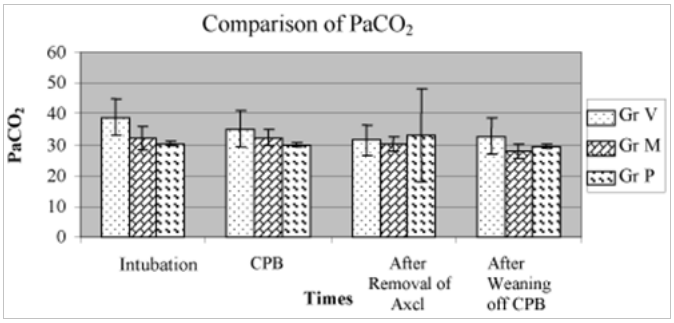

Figure 2 Comparison of PaCO2 levels in three [Group V, ventilation group; Group M, methyl prednisolone group; Group P, pentoxifylline group].

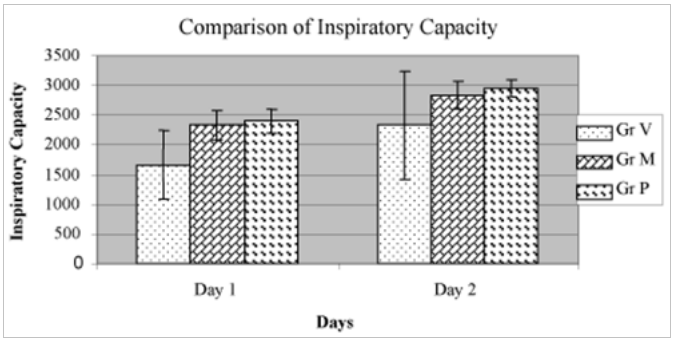

Figure 3 Comparison of inspiratory spirometry among three groups [Group V, ventilation group; Group M, methyl prednisolone group; Group P, pentoxifylline group].

Discussion

CPB induced postoperative pulmonary dysfunction is a common occurrence in ICU. In this study, authors have applied and compared three strategies of lung protection during CPB. Lung deflation during CPB is not only a major cause of atelectasis but also of reperfusion injury with restoration of normal circulation after release of aortic cross clamp. Low volume normal frequency ventilation during CPB prevents lung collapse and atelectasis thereby, reduces work for recruitment of alveoli in the post CPB period. Acute Respiratory Distress Syndrome Network.[24] demonstrated low tidal volume ventilatory strategy reduces mortality in patients with ARD Sup to 25 percent and suggested this type of ventilation may be beneficial during CPB to minimize postoperative pulmonary dysfunction. Lamarche et al.[25] concluded ventilation prevents pulmonary endothelial

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dysfunction and improves oxygenation after CPB without cross clamping in experimental animals. Mechanical ventilation prevents reperfusion induced pulmonary endothelial dysfunction after CPB. Mechanical ventilation with low tidal volume (6-8ml/kg) and high PEEP (6-9cm H2O) inhibited inflammatory cytokines release more effectively than ventilation with high tidal volume (10-12 mL/kg) and low PEEP (3-5cms H2O) in children after CPB.[26] Tidal volume employed in present study was only 2ml/kg so that it may not disturb the surgical field. Moreover there was no need to stop ventilation in any case following request from surgeons due to interference in the surgical field.

Pentoxyfylline is known to improve microcirculation, decrease platelet aggregation and plasma viscosity.[27] It inhibits formation of inflammatory cytokines, lowers leukocytes sensitivity to cytokines, and prevents neutrophil degranulation and lowers production of free radicals.[28–30] In a study, effect of 400mg Pentoxyfylline given orally thrice daily for 3days preoperatively followed by 300mg Pentoxyfylline infusion after induction of anesthesia was studied on leukocyte sequestration in lung during post CPB period and leukocyte sequestration was lower in Pentoxyfylline group than control but, alveolar arterial pO2 gradient was similar in both groups.[31] In the present study, 300mg of intravenous Pentoxyfylline infusion was administered after induction and no adverse effect was seen.

Glucocorticoids like methyl prednisolone reduce extracorporeal circuit induced inflammation, along with end organ dysfunction (myocardial, pulmonary, renal and hepatic). A single low-dose of methylprednisolone (10mg/kg) reduces the inflammatory reaction during and after CPB, by inhibition of proinflammatory cytokine release and oxygen free radical generation after release of the aortic cross-clamp.[32] In another study it was found that T-cell functions are synergistically suppressed by both extracorporeal circuit and high-dose methylprednisolone during CPB.[33] This study shows significantly better postoperative pulmonary outcome on first and second post operative day measured by inspiratory capacity, in both groups irrespective of receiving pentoxyfylline or methyl prednisolone along with low volume normal frequency ventilation during CPB. There was lower PaO2 levels during CPB in pentoxyfylline group, similar to result obtained by Clark et al.[34] The reasons for low pO2 level could be pentoxyfylline induced vasodilatation resulting in ventilation perfusion mismatch. However, the low pO2 levels were within accepted limits for pO2 during CPB and didn't produce any adverse outcome; rather patients in Pentoxyfylline group (Group P) were extubated earlier and had significantly earlier discharge from ICU than Group V. The limitations of the study was pulmonary biomarkers of inflammation specifically inhibited by Pentoxyfylline and methyl prednisolone like interleukin 1 and TNF could not be measured which could have produce supportive evidence for Pentoxyfylline or methyl prednisolone induced better postoperative lung function after CPB.

Conclusion

The anti inflammatory agents like Pentoxyfylline and methyl prednisolone prevented or reduced the inflammatory cascade of CPB induced SIRS by interfering at multiple steps and counteracting the action of the potent inflammatory interleukins and cytokines. This study concludes that low volume normal frequency ventilation along with potent anti inflammatory agents like methyl prednisolone or Pentoxyfylline may be used as lung protection strategy during CPB, and their action in lung protection is synergistic and mutually additive leading to maximal pulmonary protection during CPB. Larger studies need to be conducted along with quantitative estimation of pulmonary biomarkers of inflammation to support the cause of the authors on a sound basis of solidarity.

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None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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