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Inhaled Nitric Oxide and Prone Position: How Far They Can Improve Oxygenation in Pediatric Patients with Acute Respiratory Distress Syndrome?

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Inhaled nitric oxide (iNO) and prone position (PP) are two of the new therapeutic modalities proposed in the treatment of patients with ARDS. To test the hypothesis that PP and iNO, each acting by a different mechanism to improve arterial oxygenation, could exert safe and additive beneficial effects when used in combination, in mechanically ventilated pediatric patients with ARDS. A prospective randomized controlled study was done in pediatric intensive care unit. Thirty-two patient aged 8 weeks to 10 years with diagnosis of ARDS, on mechanical ventilation were enrolled in the study. The present study period was 24 h. Patients were divided into three groups: (1) Supine position with NO inhalation (SP+iNO), (2) Prone position without NO inhalation (PP) and (3) Prone position with NO inhalation (PP+iNO). Oxygenation parameters including, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FIO}_2$) and oxygenation index (OI) were collected at baseline (T0), 1 h (T1), 20 h (T2), 24 h (T3). In the SP+iNO group the $\text{PaO}_2/\text{FIO}_2$ ratio increased significantly from the baseline value 135 ± 8.4 mmHg at T0 to 152 ± 15 mmHg at T1 ($p = 0.05$), to 153 ± 14.1 mmHg at T2 ($p = 0.05$), then to 140 ± 13.9 mmHg at T3 ($p > 0.08$). In the PP group the $\text{PaO}_2/\text{FIO}_2$ ratio significantly increased ($p < 0.04$) from 140 ± 9 mmHg at T0 to 170 ± 10 mmHg at T1, to 185 ± 13 mmHg at T2 ($p < 0.01$) then it decreased again at T3 to 155 ± 8.5 mmHg ($p > 0.05$). While in the PP+iNO group, the $\text{PaO}_2/\text{FIO}_2$ ratio increased significantly from 139 ± 12.1 mmHg at T0 to 180 ± 12.4 mmHg at T1 ($p < 0.035$) and it continued to increase significantly to 199 ± 17 mmHg at T2 ($p < 0.005$), then it decreased again at T3 but still showing significant difference compared to T0 value (170 ± 9.5 mmHg versus 139 ± 12.1 mmHg, $p = 0.04$). Meanwhile OI in SP+iNO group decreased significantly from the baseline value 16.6 ± 1.5 at T0 to 13.1 ± 0.2 at T1 ($p < 0.05$), 12.1 ± 0.2 at T2 ($p = 0.05$) then to 15 ± 1.5 at T3 which was not significant statistically from the base line level. While in the PP group, OI decreased from 16.5 ± 1.7 at baseline to 12.6 ± 1.5 at T1 ($p < 0.05$), 10.5 ± 0.5 at T2 ($p < 0.035$), 13.9 ± 0.5 at T3 ($p > 0.05$). However in the PP+iNO group the OI decreased also significantly from 16.5 ± 1.9 at baseline to 11.5 ± 1.4 ($p = 0.03$) at T1, 9.5 ± 2.1 at T2 ($p = 0.01$) and then increased again to 11.6 ± 0.5 at T3 ($p = 0.035$). Finally analyzing the results showed that the PP+ iNO group was the one achieved best oxygenation parameters compared to base line values, with sustained significant effect even after resuming supine position and cessation of iNO. No seriously adverse events were detected during the study. The present study showed that in mechanically ventilated pediatric patients with ARDS, the combined use of PP and iNO is safe and has an additive effect, which causes a greater sustained improvement in oxygenation than either treatment strategy alone.

Key words: Acute respiratory distress syndrome, nitric oxide, prone position, pediatric patients

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INTRODUCTION

Though mechanical ventilation is fundamental in treatment of acute respiratory distress syndrome patients (ARDS) patients, adjunct treatment become crucial with the objective of optimizing oxygenation and reducing risks of high ventilator settings which may cause secondary lung lesions (Prodhan and Noviski, 2004).

Inhaled nitric oxide (iNO) and prone position (PP) are two of the new therapeutic strategies proposed for ARDS patients (Borelli *et al.*, 2000; Flores *et al.*, 2002). iNO has been shown to be beneficial in patients with ARDS by increasing arterial oxygen pressure (PaO₂) and reducing pulmonary artery pressure (Roberts *et al.*, 1992; Rossaint *et al.*, 1993). Because of its selective pulmonary vasodilatory effects, iNO improves the ventilation perfusion relationship by directing pulmonary blood flow from unventilated and perfused regions to ventilated but underperfused lung regions (Rialp *et al.*, 2001). The main concern with iNO use especially in children is the potential toxicity related to the formation of oxidative derivatives of NO, which may further worsen the lung injury (Weinberger *et al.*, 2001).

Meanwhile, PP as first suggested by Bryan (1974) is a relatively simple maneuver, that has been shown in several series to improve oxygenation and lung mechanics. PP might help to keep dependant lung areas better areated because of its more negative associated pleural pressure. This will cause improvement in arterial oxygenation due to redistribution of blood flow away from unventilated areas to regions with normal ventilation-perfusion ratio (Nakos *et al.*, 2000; Curely *et al.*, 2000). PP although proved to be an attractive therapy in children, still most of the studies are limited to the short-term effect of PP as a transient rescue maneuver, rather than a modality of treatment (Rialp *et al.*, 2001). Recently Bruno *et al.* (2001) suggested that recruitment of alveolar space performed by PP allows for enhanced effect of inhaled vasodilators and results in marked improvement of oxygenation than if they were used separately.

The current study was designed to test the hypothesis that PP and iNO, each acting by a different mechanism to improve arterial oxygenation, could exert safe and additive beneficial effects when used in combination, in mechanically ventilated, pediatric patients with ARDS.

MATERIALS AND METHODS

A prospective randomized controlled study was done in the pediatric intensive care unit (PICU) of AL-NOOR SPECIALIST HOSPITAL-KSA. During 18 month period

(November 2003 and May 2005), thirty four consecutive children aged 8 weeks to 10 years with diagnosis of acute respiratory failure, on mechanical ventilation (with positive inspiratory pressure (PIP) \geq 30 cm H₂O and fraction of inspired oxygen (FIO₂) \geq 0.5 for more than 12 h and who presented refractory hypoxemia (ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂:FIO₂) \leq 200).

The hospital ethics committee approved the study protocol and written consent was obtained from parents of all patients. Patients with cardiac or neurological disease (cyanotic), patients with chest, abdominal trauma and neurological surgeries, patients with unstable circulatory system and patients supported with extracorporeal membrane oxygenation (ECMO) were excluded from the study. All patients were monitored with the standard monitors of the PICU.

Mode of ventilation: A lung protective strategy was applied with, low tidal volume (5 to 10 mL kg⁻¹), permissive hypercapnia (PaCO₂ > 50 mmHg), as long as the arterial pH was > 7.2. Synchronized intermittent mandatory ventilation (siemens, Servo Ventilator-300A with NO cunsol) was applied to all patients, using time-cycled pressure limited or volume limited according to child weight. The general approach to improved oxygenation was initial weaning of FIO₂ to 0.5 followed by reduction in PEEP or PIP, maintaining PaO₂ > 60 mmHg.

Prone position: The patient was placed in the PP with head placed in a lateral position with the elbows flexed or extended. The pelvis was supported with a small pillow and a folded sheet was placed under the chest to allow the abdomen to be suspended. Abdominal suspension was considered an important factor in the effectiveness of prone position and was confirmed by the ability to pass a hand between the abdomen and the bed. In the present study, PP was encountered for 20 h.

Nitric oxide delivery: NO was delivered into the inspiratory limb of the patient ventilator circuit (siemens, Servo Ventilator-300A with NO cunsol), just distal to the humidifier. Flow was titrated into the circuit to deliver the prescribed level of NO. NO inhalation was used continuously for 20 h (5 ppm for 18 h then decreased to 1 ppm in the last 2 h) then discontinued regardless of its effect. Both NO and nitric dioxide (NO₂) concentration were continuously monitored with a sensor analyzer (Siemens- NO/NO₂ Monitor).

Study protocol: Thirty-two patients were enrolled in the study, which was designed to be 24 h. Following a period

of stabilization, patients were divided into three groups in which 3 different conditions were encountered to enable a comparison of the response to position and NO inhalation:

- Supine position with NO inhalation (SP+iNO)group (n = 11): in which patients were kept in SP during the 24 h study period and received NO inhalation in the first 20 h.
- PP group (n =10): patients kept in PP for 20 h then turned back to SP the remaining 4 h of the study period.
- PP + iNO group (n =11): patients kept in PP and received NO inhalation for 20 h then NO stopped and patient turned back to SP for the rest of the study period (4 h).

Oxygenation parameters presented by the ratio of PaO₂/FIO₂ and oxygenation index (OI, defined as FIO₂ ÷ mean airway pressure (MAP)/PaO₂×100), were detected for each patient at the following times:

- Time 0: or baseline data taken at the start of the study before changing patient position or administering NO.
- Time 1 and Time 2: data collected at 1 and 20 h after the start of the study.
- Time 3: data collected at the end of the study or at the 24 h point.

Also, methemoglobin concentration was measured immediately after stoppage of iNO therapy. Any critical incidents related to prone positioning or repositioning (i.e., sudden extubation, difficulty in re-intubation, dislodgement of vascular line, corneal abrasions, difficulty in ventilation, or sudden death) was reported.

Categories of responses: A positive patient response to any of the three studied conditions defined as an increase of ≥ 20 mmHg in the PaO₂: FIO₂ ratio or a decrease of ≥ 10% in the oxygenation index (OI).

The 20 mmHg supine-to-prone increase in the PaO₂: FIO₂ ratio is common measure used in research to describe a positive response to PP. The criterion of a 10% decrease in OI, although not proportionate to a 20 mmHg increase in the PaO₂:FIO₂ ratio, was added to reflect a clinically significant improvement in oxygenation that considered isolated changes in mean airway pressure (MAP).

Data analysis: Statistical analysis was done using unpaired t-test, Fisher's Exact test, chi-square test and

Wilcoxon's Rank Sum test as appropriate. A probability (P) of less than 0.05 was accepted as statistically significant. Data are expressed as mean±SD, unless stated otherwise.

RESULTS

Two patients were excluded early; one patient's PaO₂:FIO₂ ratio improved before prone positioning was achieved while another experienced deterioration of blood gas levels that precipitated multi-interventional support. Age, sex and diagnosis of remaining 32 patients enrolled in the study were comparable and summarized in Table 1.

The median duration of mechanical ventilation preceding the PP was 24 h (10-60 h). The median duration of time from the recording of the first PaO₂: FIO₂ ratio below 200 mmHg to the PP was 15 h (5-45 h). At baseline, neuromuscular blocking agents were used to facilitate mechanical ventilation in 40% of patients. Forty five percent of patients were receiving at least one vasoactive drug to support their hemodynamic function. All patients were sedated with a combination of a benzodiazepine and a narcotic.

In all the studied groups, baseline values of PaO₂:FIO₂ and OI were compared with values at 1, 20 and 24 h.

Figure 1 showed the PaO₂:FIO₂ ratio obtained in the three groups during the whole 24 h study period. In the SP+iNO group the PaO₂:FIO₂ ratio increased significantly from the baseline value 135±8.4 mmHg (time 0) to 152±15 mmHg at time 1 (p = 0.05), to 153±14.1 mmHg at time 2 (p = 0.05), then to 140±13.9 mmHg at time 3 (p>0.08). In the PP group the PaO₂:FIO₂ ratio significantly increased (p<0.04) from 140±9 mmHg at time 0 to 170±0 mmHg at time 1, to 185±13 mmHg at time 2 (p<0.01) then it decreased again at time 3 to 155±8.5 mmHg (p>0.05). While in the PP+iNO group, the PaO₂:FIO₂ ratio increased significantly from 139±12.1 mmHg at time 0 to 180±12.4 mmHg at time 1 (p<0.035) and it continued to increase significantly to 199±17 mmHg at time 2 (p<0.005),

Table 1: Results of age, sex primary diagnosis of studied patients

Variables	SP+iNO (n=11)	PP (n=10)	PP+iNO (n=11)	p-value	
Age	In months	11	13	12	>0.05
	median range	(10-113)	(8-115)	(9-119)	
Gender	Male	7	5	6	>0.05
	Female	4	5	5	
Primary diagnosis	Sepsis/septic shock	4	4	5	>0.05
	Pneumonia	5	3	4	>0.05
	Drowning	1	1	0	>0.05
	Inhalation injury	1	2	2	>0.05

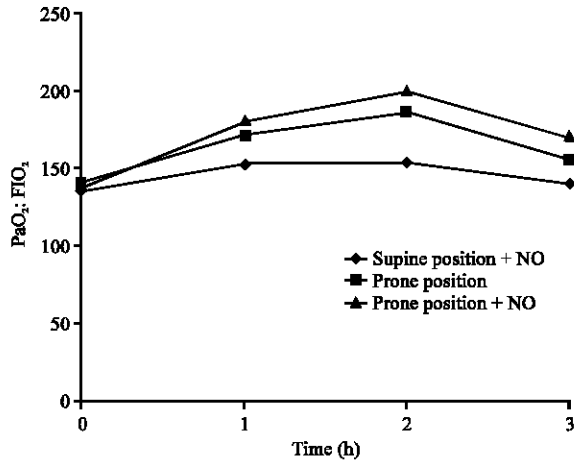


Fig. 1: PaO₂:FIO₂ in the three studied groups

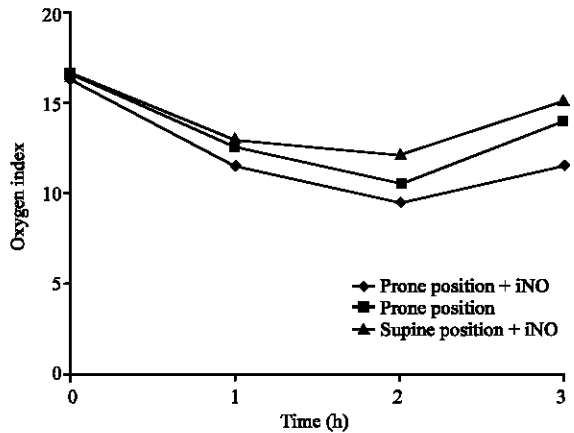


Fig. 2: Oxygen index in the three studied groups during the study period

then it decreased again at time 3 but still showing significant difference compared to time 0 value (170±9.5 mmHg versus 139±12.1 mmHg, p = 0.04).

Figure 2 showed the oxygen index (OI) in the three groups during the 24 h study period at four data collection points. In the SP+iNO group OI decreased significantly from the baseline value 16.6±1.5 to 13.1±0.2 at time 1 (p<0.05), 12.1±0.2 at time 2 (p = 0.05) then to 15±1.5 at time 3 which was not significant statistically from the base line level. While in the PP group, OI decreased from 16.5±1.7 at baseline to 12.6±1.5 at time 1 (p<0.05), 10.5±0.5 (p<0.035) time 2, 13.9±0.5 at time 3 (p>0.05). However in the PP + iNO group the OI decreased also significantly from 16.5±1.9 at baseline to 11.5±1.4 (p = 0.03), 9.5±2.1 at time 2 (p = 0.01) and then increased again to 11.6±0.5 at time 3 (p = 0.035).

By observing the above two figures, it is obvious that the PP + iNO group was the one achieved best oxygenation parameters with sustained significant effect even after resuming supine position and cessation of iNO.

There were no serious adverse events during iNO administration. Methemoglobin concentrations did not rise above 1% of total hemoglobin in any child and maximum nitric dioxide (NO₂) concentration measured was 1.5 ppm. No critical incidents related to positioning or repositioning occurred during the study period.

DISCUSSION

The current study confirms that PP and iNO are useful therapeutic tools that improve oxygenation in pediatric patients with ARDS, without inducing short-term adverse effects.

Inhaled NO has been shown to improve oxygenation in adults and children with ARDS (Trony *et al.*, 1998). The physiologic basis of this effect is the selective pulmonary vasodilation that occurs with iNO, resulting in reduced pulmonary vascular resistance and better ventilation/perfusion (V/Q) ratio. However the improvement in oxygenation has been described as trivial, short lived and clinically unimpressive (Krafft *et al.*, 1996). Even prolonged therapy of iNO may have limited therapeutic role in children with acute hypoxemic respiratory failure as it could not achieve sustained improvement in oxygenation (Day *et al.*, 1997).

Fioretto *et al.* (2004) showed that iNO in low doses (5 ppm), is safe for use in children and concluded that early treatment with iNO causes acute and sustained improvement in oxygenation, with earlier reduction in ventilator settings. Supporting the results of Fioretto, the current study showed almost immediate improvement in oxygenation induced by early treatment with iNO (5 ppm) which achieve a rapid steady state. However, stoppage of iNO in the present study resulted in regression of oxygenation indexes to nearly the base line values. Taylor *et al.* (2004), reported that iNO in patients with acute lung injury resulted in short-term oxygenation improvement with no impact on the duration of ventilatory support or mortality. Several reports explained the response to iNO in ARDS patients to be quite variable, unpredictable, depending on the nature and severity of the underlying lung disease and no specific dose of iNO proved to be more advantageous than any other (Kornecki *et al.*, 2001; Sokol *et al.*, 2003).

Not only NO but also PP is one of several alternatives proposed to improve oxygenation in children suffering from sever hypoxemia (Bruno *et al.*, 2001). Fridrich *et al.* (1996), reported that 20 h PP protocol was necessary to improve oxygenation in their critically ill adult patients. Other investigators concluded that the duration of PP (12 h/day) is important for the beneficial effect of this maneuver and they suggested that PP should be the preferred position for the management of oxygenation failure in children (Kornecki *et al.*, 2001). Considering

these previous results, we designed our study to keep patients in PP for 20 h then finish the 24 h study period in SP (once daily prone position protocol). Returning patients to SP for 4 h/day does allow sufficient time for skin assessment and bed making. Improvement in oxygenation could be confirmed in the present study when turned the patients from supine to prone position. This goes with that of Curley *et al.* (2000) who support the use of repeated prone positioning (20 h/day until improvement or death) as a therapeutic intervention to improve systemic oxygenation in pediatric patients with ARDS. However Numa *et al.* (1997), failed to show such improvement in oxygenation in their pediatric patients with ARDS, which may be due to the short time PP (1 h) and may be also due to long duration of mechanical ventilation (mean, 11.9 days) prior to the use of PP. Improvement of oxygenation in the current study occurred in most of the patients in the first hour except for two patients with mild transient deterioration. This goes concomitantly with others who postulated that if an improvement in oxygenation does occur, it appears within the 30 min, or at least in first 2 h (Mur *et al.*, 1997; Chatte *et al.*, 1997; Kornecki *et al.*, 2001). Curley *et al.* (2000) who observed that 80% of their studied children had improved oxygenation immediately after turning them to PP suggested that the optimal response and beneficial effect of PP might be most likely during the early edematous phase of ARDS, when lung edema and atelectasis predominate. In the current study persistent improvement of oxygenation during PP corroborate the hypothesis that duration of PP is important for the beneficial effect of this maneuver, also it may suggest that PP has a prolonged beneficial effect (Fridrich *et al.*, 1996; Korneck *et al.*, 2001). Meanwhile regression in oxygenation parameters after turning patients back to SP supports the results of Papazian *et al.* (1998), who found no persistent improvement in oxygenation for 6 h. after turning patients to SP and explained it by the fact that repositioning patients in SP restores the gravitational retro-dorsal gradient. Therefore, after a few hours, it was not surprising to observe a decrease in oxygenation due to the decrease in ventilation of the posterior part of the lung. On contrary Curley *et al.* (2000), reported persistent improvement in oxygenation after a return to the supine position specifically in the immediate responders subset and attributed it to the cumulative effect of prolonged PP on oxygenation.

Of note the interesting point in the current study is that although iNO or PP used separately achieves significant, non-persistent improvement in oxygenation but iNO and PP used in combination could achieve best oxygenation parameters with sustained significant effect even after resuming supine position and cessation of iNO (Fig. 1 and 2).

Papazian *et al.* (1998) could prove that the association between iNO and PP presents an additive effect on oxygenation. In contrast, others detected no improvement in oxygenation in response to iNO in any one of his patients regardless of position, which may be attributed to the short duration of exposure (40 min) of iNO (Kornecki *et al.*, 2001).

Borelli *et al.* (2000), suggested that a strategy including both iNO and PP could warrant the best improvement in oxygenation in ARDS patients. The possibility of the additive effect of both modalities with resultant marked improvements in oxygenation could be explained by the fact that recruitment of alveolar space promoted by PP allows for enhanced effect of inhaled vasodilators, such as nitric oxide (Bruno *et al.*, 2001; Rialp *et al.*, 2001; Johannigman *et al.*, 2001).

Finally, concerns regarding toxicity of iNO and adverse effects of PP was considered in the current study. NO toxicity is mainly related to the formation of NO₂ and methemoglobin. NO₂ is known to be a potent pulmonary irritant and its production rate depends on iNO dose, FIO₂ and length of NO treatment (Fioretto *et al.*, 2004). Meanwhile the reaction of NO with hemoglobin produces methemoglobin which can adversely affect tissue oxygenation. The binding and formation of methHB is concentration-and time-dependant (Weinberger *et al.*, 2001). Results of the present study showed that methemoglobin concentrations did not rise above 1% of total hemoglobin and maximum nitric dioxide (NO₂) concentration measured was 1.5 ppm. This goes with the recommendations of Occupational Safety and Health Administration who limits human peak exposure of NO₂ to 5 ppm (Centers for Disease Control, 1988). Also with that of Fioretto *et al.* (2004) who proved that methemoglobin concentration >2% of total hemoglobin can impair oxygen unloading and worsen tissue hypoxia.

Also, pp could be accomplished safely in the present study with no reported critical incidents. This supports experience of other investigators (Curely *et al.*, 2000) who demonstrated that patients in PP (20 h/day) could be effectively ventilated and weaned from mechanical ventilation successfully and safely without critical incidents or physiologic compromise.

CONCLUSIONS

In mechanically ventilated pediatric patients with ARDS, the use of combined iNO and PP is safe and their additive effect resulted in a significant pronounced and persistent improvement in oxygenation parameters than those observed when iNO or PP used separately. Therefore, we suggest that these two therapies in combination should be considered as important and safe adjuncts to mechanical ventilation in pediatric patients with refractory hypoxemia.

REFERENCES

- Borelli, M., L. Lampati, E. Vascotto, R. Fumagalli and A. Pasenti, 2000. Hemodynamic and gas exchange response to inhaled nitric oxide and prone positioning in acute respiratory distress syndrome patients. *Crit. Care Med.*, 28: 3083-3084.
- Bruno, F., J. Piva, P. Garcia, P. Einloff, R. Fiori and S. Barreto, 2001. Short-term effects of prone positioning on oxygenation of pediatric patients submitted to mechanical ventilation. *J. Pediatric. (Rio. J.)*, 77: 361-368.
- Bryan, A.C., 1974. Comments of a devil's advocate. *Am. Rev. Respir. Dis.*, 110: 143-144.
- Centers for Disease Control, 1988. Recommendations for occupational safety and health standards. *Morbidity Mortal. Wkly. Rep.*, 37: 21.
- Chatte, G., J.M. Sab and J. Dubois *et al.*, 1997. Prone position in mechanically ventilated patients with severe acute respiratory failure. *Am. J. Respir. Crit. Care Med.*, 155: 473-478.
- Curley, A.M., E.J. Thompson and J. Arnold, 2000. The effects of early and repeated prone positioning in pediatric patients with acute lung injury. *Chest*, 118: 156-163.
- Day, R.W., E. Allen and M.K. Witte, 1997. A randomized, controlled study of the 1 and 24 h effects of inhaled nitric oxide therapy in children with acute hypoxemic respiratory failure. *Chest*, 112: 1324-1331.
- Fioretto, J.R., M. Moraes, R. Bonatto, S. Richetti and M. Capri, 2004. Acute and sustained effects of early administration of inhaled nitric oxide to children with acute respiratory distress syndrome. *Pediatr. Crit. Care Med.*, 5: 469-474.
- Flores, C., M. Azagra, R. Lopez and A. Serrano, 2002. Pediatric ARDS: Effect of supine-prone postural changes on oxygenation. *Intensive Care Med.*, 28: 1792-1796.
- Fridrich, P., P. Krafft and H. Hochleuthner, 1996. The effects of long-term prone positioning in patients with trauma-induced adult respiratory distress syndrome. *Anesth. Analg.*, 83: 1206-1211.
- Johannigman, J.A., K. Davis, S. Miller and R. Campbell *et al.*, 2001. Prone positioning and inhaled nitric oxide: Synergistic therapies for acute respiratory distress syndrome. *J. Trauma*, 50: 589-595.
- Komecki, A., H. Frndova, A. Coates and S. Shemie, 2001. A randomized trial of prolonged prone positioning in children with acute respiratory failure. *Chest*, 119: 211-218.
- Krafft, P.P., R.D. Fridich and D. Fitzgerald *et al.*, 1996. Effectiveness of nitric oxide inhalation in septic ARDS. *Chest*, 109: 486-493.
- Mur, M., C.R. Martling and S. Lindahl, 1997. Dramatic effect on oxygenation in patients with severe acute lung insufficiency treated in prone position. *Crit. Care Med.*, 25: 1539-1544.
- Nakos, G., I. Tsangaris, E. Kostanti, C. Nathanail, A. Lachana and V. Koulouras, 2000. Effect of the prone position on patients with hydrostatic pulmonary edema compared with patients with acute respiratory distress syndrome and pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.*, 161: 360-368.
- Numa, A.H., J. Hammer and C.J. Newth, 1997. Effect of prone and supine positions on functional residual capacity, oxygenation and respiratory mechanics in ventilated infants and children. *Am. J. Respir. Crit. Care Med.*, 56: 1185-1189.
- Papazian, L., F. Bregeon, F. Gaillat, X. Thirion, M. Gainnier and R. Gregoire *et al.*, 1998. Respective and combined effects of prone position and inhaled nitric oxide in patients with acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.*, 157: 580-585.
- Prodhan, P. and N. Noviski, 2004. Pediatric acute hypoxemic respiratory failure: Management of oxygenation. *J. Intensive Care Med.*, 19: 140-153.
- Rialp, G., A. Betbese, M. Perez-Marquez and J. Mancebo, 2001. Short-term effects of inhaled nitric oxide and prone position in pulmonary and extrapulmonary acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.*, 164: 243-249.
- Roberts, J., D. Polaner, P. Lang and W. Zapol, 1992. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. *Lancet*, 340: 818-819.
- Rossaint, R., K. Falke, F. Lopez, K. Salama, U. Pison and W. Zapol, 1993. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl. J. Med.*, 328: 399-405.
- Sokol, J., S. Jacobs and D. Bohn, 2003. Inhaled nitric oxide for acute hypoxic respiratory failure in children and adults: A meta-analysis. *Anesth. Analg.*, 97: 989-998.
- Taylor, R., L. Zimmerman, D. Phillip, R. Straube and G. Criner *et al.*, 2004. Low-dose inhaled nitric oxide in patients with acute lung injury. *JAMA.*, 291: 1-3.
- Trony, E., J.P. Collet and S. Shapiro *et al.*, 1998. Inhaled nitric oxide in acute respiratory distress syndrome: A pilot randomized controlled study. *Am. J. Respir. Crit. Care Med.*, 157: 1483-1488.
- Weinberger, B., D. Laskin, D. Heek and J. Laskin, 2001. The toxicology of inhaled nitric oxide. *Toxicol. Sci.*, 59: 5-16.