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Food: A Causal Nexus for Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome is an unfortunate occurrence and once diagnosed, outlook is bleak with survival rates of approximately 60%. As such, it is of great interest to determine the standard of care and possible novel treatments for the future. Novel treatments of interest include mesenchymal stem cells, ghrelin and high-frequency ventilation. In a phase 1 clinical trial, mesenchymal stem cells have shown great promise in efficacy while being well-tolerated in patients. In addition, while ghrelin has only shown to be effective in animal models, it shows promise for further studies. At the same time, the effectiveness of corticosteroids, which has been the standard of care along with antibiotics, has been questioned with studies indicating success while others demonstrate a lack of efficacy.

Anesthesia is complicated. Consciousness and the art of its artificial rendering are delicate. The risks are inherent but necessary ones. Nil per os is a phrase that strikes annoyance in the hearts of patients worldwide but not many understand its implications. Emesis is a nightmare for both patient and anesthesiologist. If it occurs while under the influence of anesthesia, life-threatening conditions such as sepsis or Acute Respiratory Distress Syndrome (ARDS) can develop when a patient intentionally or unintentionally fails to follow nil per os and survival rates in such cases have been observed at less than 60% [1]. Prevention by active communication between the patient and the health care team can help alleviate this risk. However, the development of a novel treatment for such a dangerous condition is necessary. In the event of sepsis, anesthesia is traditionally contraindicated to prevent systemic disease. However, recent research shows that this may not be the case [2].

Sepsis has been found to be the most common etiology of ARDS. In a study done by Singh et al. [1] it shows that in 34.6% of patients with ARDS, the condition develops as a result of sepsis. Unsurprisingly, sepsis combined with major thoracoabdominal surgeries result in a 60% incidence rate of ARDS. Finally, patients who have failed to follow *nil per os* and experienced a gastric aspiration resulted in the highest incidence rate of ARDS at 62.5%. Approximately 42% of the ARDS cases in the particular study were fatal according to the NAECC criteria for ARDS [3].

Current treatments of ARDS include corticosteroids, mechanical ventilation and as with any condition caused or aggravated by sepsis, antibiotics are prescribed. Nitric oxide and surfactants are used to normally increase the fraction of inspired oxygen and augment gas exchange. However, their effectiveness in treating ARDS is still under investigation [4]. The most common bacteria found in sepsis are *Enterococcus spp., Enterobacteriaceae, Staphylococcus aureus, coagulase-negative staphylococci, Pseudomonas aeruginosa, and Acinetobacter baumannii* [5]. The WHO recommends a combination of benzylpenicillin/ampicillin and gentamicin, a combination of chloramphenicol and benzylpenicillin or third-generation cephalosporins [6]. An addition of clavulanic acid can be considered if the sepsis is known to be caused by β-lactam antibiotic resistant strains of bacteria. Third-generation cephalosporins are not as effective against gram-positive bacteria compared to the first generation as a trade-off for having increased activity against gram-negative bacteria. It would be favorable to identify specific strains for more effective narrow-spectrum antibiotics.

Mechanical ventilation is the front-line treatment for ARDS as it supports effective oxygenation but comes with its own risks. Conventional mechanical ventilation uses higher tidal volumes compared to high-frequency ventilation which can result in Ventilator-Associated Lung Injury (VALI) by way of pulmonary volutrauma. Parts of the lungs that suffer from atelectasis under traditional ventilation are under-inflated while the healthy lung parenchyma are over-inflated resulting in VALI. A lower tidal volume is also non-ideal as it can result in permissive hypercapnia. High-frequency ventilation allows a lower tidal volume while reducing dead space. In theory, this should allow more optimal oxygenation and thus recovery from ARDS. Studies have indeed shown this to be the case. Mortality and morbidity were significantly reduced and less likely with p-values of 0.03 and 0.04 respectively [7].

The use of corticosteroids to treat ARDS and has been a disputed topic. Because corticosteroids regulate inflammation, they have often been used to treat ARDS. Various forms of dosages at different stages of ARDS have been tested in different studies. One particular study has shown that early administration (within 48 hours of diagnosis) of low dose corticosteroids to patients was not associated with decreased mortality. In the

study, 1,838 patients who received low dosage treatment were matched to a control group of 1,838 patients of equal severity of illness with mortality rates in a 30 day time frame of only 35.5% vs 34.9% respectively ($p \leq 0.77$) [8]. Based on the insignificant p-value, it was concluded that there was little significance in early administration of low-dosage corticosteroids in treatment of septic patients. However, after further inspection, patients with severe septic shock (APACHE II score above 30), seemed to respond more positively to low-dosage corticosteroids ($p \leq 0.02$). The possibility of a high dosage corticosteroid treatment has been considered in a review done by Deal et al. [9] which found no resounding success in studies that examine short-term high dosage administrations of corticosteroids to treat early onset ARDS or prevent ARDS [9]. As for long-term low dosage administrations of corticosteroids, the review encountered conflicting results; one study showing 13% mortality of patients receiving corticosteroids and 68% mortality in the control ($p \leq 0.03$) and another study showing no significant differences at 29.2% vs. 28.6%. Evidently, the treatment of ARDS/sepsis through the use of corticosteroids has been generally ineffective in the short run, with inconclusive results amongst studies involving corticosteroids in low dosages.

For such a syndrome with high mortality and morbidity rate, effective treatment has remained largely intangible to medical professionals and researchers. Alternatives are needed and one that has shown promise is the administration of Mesenchymal Stem Cells (MSCs). Multipotent mesenchymal stem cells (stromal cells) have demonstrated potential in treating both ARDS as a result of sepsis and sepsis itself [10]. While MSC treatments have been previously primarily explored for their ability to engraft at sites of direct tissue damage, research suggests that they may contain mechanisms that produce therapeutic effects in instances of sepsis, acute respiratory distress syndrome and other sepsis related complications [4].

Several characteristics are possessed by mesenchymal stem cells which render them favorable for treatment of many acute inflammatory syndromes. MSCs are considered non-immunogenic due to their low constitutive expression of Major Histocompatibility Complex (MHC) type I and their complete lack of MHC type II and T-cell co-stimulatory molecules. This prevents an immune response of the host system that could exacerbate existing conditions or create more concerning acute symptoms. No Human Leukocyte Antigen (HLA) matching or immunosuppression would be needed in the application of MSCs as a therapeutic measure through an allogeneic transplant from a donor. This makes the therapy comparatively efficient in regard to initial treatment application. MSCs also have a low likelihood to produce tumors, unlike embryonic stem cells which have also been explored as a potential treatment, and a short in-vivo lifespan [4]. Current research shows that MSCs exhibit immunomodulatory, antimicrobial and anti-inflammatory effects, allowing them to regulate important pathobiological pathways in the onset and development of sepsis and ARDS. Tested pathways include epithelial and endothelial cell injury in both conditions and removal of alveolar edema fluid in ARDS. MSCs can also transfer mitochondria to injured epithelial cells [11]. These characteristics of MSCs are attributed to the release of paracrine factors as studied in ex-vivo isolated perfused human lung models by Wilson et al.[11] in the START, or stem cells for ARDS treatment, trials [10]. Research revealing that MSC therapy may have the potential to reduce infection severity and improve tissue repair in the alveoli after injury makes them an attractive novel therapy for patients suffering from ARDS and sepsis resulting from bacterial infection [10].

After the successful pre-clinical trials done on mice, rats, sheep and ex-vivo lung models in the START program; subsequent related clinical trials have shown promising results. The phase 1 clinical trial, performed by Wilson et al. [11] tested single-dose safety of allogeneic bone marrow-derived MSCs in patients with ARDS that was considered moderate to severe excluding those for which 96 hours had passed since their consideration of meeting the Berlin definition of ARDS since MSC therapy needed to be implemented within 120 hours of official diagnosis. According to the study, all 9 patients tested took well to the infusion and exhibited no infusion-associated adverse effects. None exhibited instability during the first seven days post-administration of MSCs. Between baseline and day 3, all experimental groups including US Food and Drug Administration approved "low dose," "intermediate dose," and "high dose" MSC infusion groups, experienced an improvement in mean Lung Injury Score (LIS) and a decline in mean Sequential Organ Failure Assessment (SOFA). However, within 60 days of the infusion, two of the nine patients studied developed serious adverse effects resulting in death. One patient death occurred in the "low dose" group and one in the "intermediate dose" group leading to an estimated mortality rate 22% for the trial. After thorough investigation by both the Scientific Review Committee and Data Safety Monitoring Board (comprised of critical care physicians and a clinically experienced biostatistician), these deaths were deemed completely unrelated to the MSC infusion and were instead attributed to the patients' prior condition. Primary outcomes insist that all three sequential doses up to 10 million cells/kg predicted bodyweight are safe for use in patients with moderate-to-severe ARDS. The 22% mortality rate exhibited in the study was significantly lower than the projected rate of survival for patients with moderate ARDS (32%), as indicated by the Berlin severity stages. According to Wilson et al. [11] this rate is fairly consistent with other reported survival rates in patients with similar starting LIS scores (lower by 1%). While optimum dose of MSCs remains unclear, the study concluded that MSC infusion caused no adverse effects in receiving patients and may have the potential to improve survival rate in ARDS patients pending a phase 2 trials [11].

Another recent development in the treatment of ARDS and sepsis has been found in ghrelin. Ghrelin is a hormone produced by ghrelin cells that regulates mainly hunger and energy-homeostasis. Research has shown that its role in the body is much more complex than previously thought. A particular study done by Wei et al. [12] has shown that ghrelin can inhibit proinflammatory responses in rats with sepsis [12]. It was shown that ghrelin had significantly lowered the levels of proinflammatory cytokines

and in addition inhibited the activation of caspase-3 in the hippocampus after cecal ligation and puncture. Injecting ghrelin within 4 to 16 hours of induced sepsis seemed to treat symptoms of sepsis effectively. Interestingly, there have been studies linking ghrelin and MSC cell differentiation, however, there is not adequate evidence in the context of medical applications of MSCs linked with ghrelin to make any relevant assumptions about their potential role in a dual treatment [13].

While the treatment of ARDS is critical, determining how sepsis and infection affects anesthesia in patients is also significant. Infection is a risk factor that cannot be negated in procedures where anesthesia is necessary. In patients with periprosthetic joint infection, patients given neuraxial anesthesia had lower odds of systemic infection versus general anesthesia with rates of infection at 4% and 12% respectively [2]. While it may be the nature of the joint infection itself, it is worthwhile to consider potentially contraindicate general anesthesia if neuraxial anesthesia is a viable alternative in the event of infection. However, it has also been shown that neuroaxial blocks may be difficult to reverse in septic patients [14]. With regional anesthesia, extra precaution should be taken against coagulopathy as a result of systemic infection and sepsis. In addition, early hemodynamic optimization prior to organ failure of septic patients has been shown to reduce mortality by 23% when compared to optimization after organ failure [15]. A peripheral nerve block should be considered when it is desirable to prevent a sympathetic response from a painful stimulus without the systemic effects of opioids in patients with sepsis. Multiple risk factors can contradict and contraindicate with possible anesthetic options and additional precaution should be practiced in this event.

In conclusion, as ARDS continues to cause high mortality rates, it is of great interest to reduce the rate by any means possible. High-frequency ventilation, coupled with antibiotics and corticosteroids are a good first-line of defense for ARDS but better potential treatments may exist such as ghrelin and mesenchymal stem cells pending larger clinical trials. In discussing the effect of ARDS on patients, it would be remiss not to discuss sepsis' effect on anesthesia. As shown, sepsis can contraindicate some anesthetic options leaving other options more desirable. In the continued fight against ARDS, the pursuit for the optimal protocol is slowly being elucidated.

Disclaimer

The views expressed in this paper represents the views of the authors and are not officially endorsed by the institution.

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