[연구계획서]

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1. **배경**
   1. 최근 소아에서는 Septic shock에서의 ECMO의 치료적 효과에 대한 연구들이 발표되고 있다. (Sole, 2018)
   2. 성인에서의 Septic shock에서의 ECMO의 치료적 효과에 대한 연구에서는 생존율을 7-70%로 다양하게 보고되고 있으며 논쟁의 여지가 있다.
      1. Sepsis에 의한 distributive shock에서는 예후가 좋지 않으나, sepsis-related SCMP에서는 좋은 예후를 보인다.
   3. ﻿미국 Society of Critical Care Medicine (SCCM)과 유럽의 European Society of Intensive Care Medicine (ESICM)에서 2016년에 패혈증에 대한 새로운 정의인 “SEPSIS-3”를 발표했다. (Singer, 2016)
      1. Infection의 증거 (이에 대한 구체적인 내용은 없음) AND SOFA score 2점 이상 증가
2. **최근 연구들**
   1. Park TK (EJCTS, 2015) - SMC
      1. Retrospective, Jan 2005 - Dec 2013
      2. Study population: N=32 - adults >18, ECMO for sepsis
         1. Sepsis 정의 - clinical sign of infection + evidence of microorganism (culture or serology)
      3. primary outcome - survival to hospital discharge
         1. survivor - lower peak **lactate** (p=0.03), lower **SOFA** at day 3 (p=0.01), higher **Troponin I** (p=0.02)
         2. Multivariable Cox PH regression
            1. **CPR** (aHR 4.61 p=0.006), **TnI** >15 (aHR 0.34, p=0.04)
      4. Conclusion
         1. Survival to hospital discharge - low in adult patients with refractory septic shock despite ECMO support
         2. might be beneficial in severe myocardial injury during septic shock
         3. but should be avoided in patients who have received CPR
   2. Ro SK (JTCS, 2018) - 아산
      1. Study population
         1. main cohort: 71 consecutive, septic shock + VA-ECMO
            1. prospectively registered in ECMO database
            2. retrospectively reviewed
            3. adults, 2005-2012, VA-ECMO for septic shock
         2. control: 253 cardiogenic shock + VA-ECMO
      2. Definition
         1. Severe sepsis - acute organ dysfunction d/t infection
         2. septic shock - sepsis with hypotension NOT reversed by fluid resuscitation
      3. Results
         1. Primary outcomes - weaning and survival outcomes
            1. weaning 11/71 (15.5%) from ECMO
            2. survival to discharge 5/71 (7.0%)
         2. Survivors vs. non-survivors in target
            1. Pre-/6 hours lactate levels - higher in the nonsurvivors (P=0.036, P=0.002)
         3. Septic shock vs. Cardiogenic shock
            1. Rates of successful weaning (p<0.001)
            2. Survival to discharge (p<0.001)
      4. Conclusion
         1. Poor outcomes of ECMO in refractory septic shock
         2. Elevated arterial **lactate** levels pre-/post-ECMO – a/w risk of in-hospital death
   3. Cheng A (JTCS, 2016)
      1. Study population
         1. ECMO registry - 2001 ~ 2011
         2. 151 adults (>=16 y) & ECMO for life-threatening sepsis
            1. 정의: infection-related ARDS or severe septic shock refractory to maximal conventional therapy
      2. Results
         1. main types of infection - pneumonia (50%), myocarditis (20%), primary bloodstream infections (15%)
            1. non-fermentative Gram-negative bacteria (NFGNB) (26%), Entero- bacteriaceae (24%), and Gram-positive cocci (21%)
         2. Multivariable Cox-proportional hazards model
            1. R/F: **age**>75 years (HR 1.98, 95% CI 1.30-3.02), **pre-ECMO dialysis** (HR 3.20, 95% CI 1.34-7.63), longer door-to-ECMO intervals (HR 1.01, 95% CI 1.00-1.02), venoarterial mode (HR 2.58, 95% CI 1.55-4.21), fungal (HR, 2.83, 95% CI, 1.36- 5.88) & NFGNB sepsis (HR, 2.48, 95% CI, 1.44-4.27)
            2. Protective factor: Gram-positive sepsis (HR, 0.20, 95% CI, 0.08-0.57), myocarditis (HR, 0.12, 95% CI, 0.06-0.27), pneumonia (HR, 0.54, 95% CI, 0.30-0.90), effective empirical antimicrobial therapy (HR, 0.57, 95% CI, 0.37-0.89)
         3. Outcomes
            1. ECMO survival 54%
            2. survival to discharge 42%
            3. door-to-ECMO <= 96 hours (P<.0001)

cutoff by ROC - 3.8 days

* + 1. Conclusion
       1. Better outcomes - door-to ECMO times <= 96 hours, Gram-positive (rather than Gram-negative sepsis), pneumonia (rather than primary bloodstream infections)
  1. Sole A (EJP, 2018)
     1. Study population
        1. retrospective
        2. Inclusion criteria
           1. refractory septic shock ≤18 years old + VA ECMO
        3. Exclusion
           1. infection after ECMO, ECMO for non-septic causes, ECMO mainly d/t respiratory faliure secondary to infection
     2. Outcomes
        1. mortality at hospital D/C, neurologic Cx., total dasy on ECMO, days on MV, ICU LOS
     3. Results
        1. 21 patients included
           1. 13 (65%): male
           2. 9 pediatric & 12 newborns
           3. Median septic shock duration prior to ECMO: 29.5 h (IQR, 20–46)
           4. 11 (52.4%) cardiac arrest
           5. S. agalctiae (GBS) - m/c, 33% in newborns
        2. Neonatal vs. Pediatrics
           1. Neonatal - worse SOFA, OI, P/F ratio, ABGA, lactate, LVEF
        3. Survival
           1. pedi - 33.3% (60% w/o pneumococcal cases) vs. newborns - 50%
           2. survivor vs. non-survivor

Hours of sepsis evolution, mean airway pressure - higher in the non-survivor group

* + - * 1. mortality risk factor

Streptococcus pneumoniae infection

NO other independent R/F for mortality from multivariate analysis

* + - 1. 2001-2008 vs. 2009-2017
         1. improved survival during the second period - from 14.3 to 57.2%

shorter sepsis evolution before ECMO placement, better candidate selection, and greater ECMO support

* + 1. Conclusion
       1. ECMO as considerable option for refractory septic shock in pedatrics
       2. should be used with caution in vasoplegic pattern shock, gram-negative infection, or S. pneumoniae sepsis

1. **연구목적**
   1. ECMO 환자에서 sepsis가 미치는 영향에 대해 살펴보고자 한다.
2. **연구설계**
   1. 대상환자
      1. Inclusion criteria - SMC에서 시행한 모든 종류의 성인 ECMO 환자
      2. 환자군
         1. Group 1: Sepsis 환자에서 ECMO insertion을 시행한 경우
            1. (예상 환자군: pneumonia ARDS w/ VV-ECMO, VA-ECMO for septic shock)
         2. Group 2: ECMO 시작 후 sepsis 진단
            1. Sepsis 진단은 Sepsis-3 진단기준을 따름
         3. Group 3: Non-septic ECMO
            1. 다른 이유로 ECMO 삽입 AND ECMO 종료시점까지 sepsis 진단되지 않음
   2. 자료수집 - 단일연구기관, 후향적 의무기록 조사
   3. 변수
      1. Baseline
         1. 기본 변수
            1. age, gender
            2. LFT, RFT 등등
         2. ECMO 관련
            1. PreECMO CPR
            2. 삽입 이유
            3. Configuration
            4. Serial DIC lab
            5. Troponin I
            6. Echo상 LV dysfunction or RV dysfunction
         3. Infection 관련
            1. WBC, CRP, procalcitonin
            2. Culture
            3. Serial SOFA score
            4. Serial lactate
            5. SvO2 (VV ECMO에서는 신뢰도 저하)
   4. **Outcomes**
      1. **Primary Outcomes – group 간 생존률 차이 분석**
         1. 예상) Group 3 가 가장 좋을 것으로 생각됨. Group 1 vs. Group 2?
      2. **Secondary Outcome**
         1. **Group 2내 위험인자 분석**
         2. **Group 2-3 비교 - Sepsis 발생 예측인자 (?)**
            1. 예상) 당연히 infection, organ dysfunction lab (AST, ALT, Cr)등 (SOFA score 관련 변수들)이 유의하게 나올 듯
   5. 분석 방법
      1. Primary outcomes
         1. Group 간 KM 및 log-rank test
      2. Secondary outcomes
         1. Group 2내 Multivariable Cox regression
3. **연구 활용 방안**
   1. ECMO 환자관리 중 sepsis가 환자에게 미치는 예후를 예측하며, 이에 대한 위험인자들을 조기에 발견하고 교정할 수 있도록 한다.