Survival in Refractory Septic Shock: Comparison between Usual Management, Methylene Blue, and Terlipressin: A Pilot Study

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Background: Refractory septic shock cases usually develop catecholamine resistant. Vasopressin is recommended as additional vasopressor after norepinephrine (NE), but it’s not available in Thailand. From previous studies, both terlipressin and methylene blue are reported as effective vasopressors in septic shock.

Objective: To compare outcomes in refractory septic shock patients between usual management, and addition of methylene blue, or terlipressin.

Method: This is a single center randomized controlled trial, involving patients with refractory septic shock (NE ≥ 0.5 µg/kg/min) in intensive care unit. Patients were randomized into 3 groups: usual treatment (control), methylene blue (MB group), and terlipressin (TP group). Primary outcomes of the study were survival rate at 7 days and 28 days.

Result: There were 17 cases of refractory septic shock (6 in control group, 5 in MB group, and 6 in TP group). Median age of control, MB, and TP groups were 69.5 years (IQR 49-78), 59 years (50-64), and 62 years (55-83), respectively. Median APACHE score were 29.5 (23-44) in the control, 29 (28-30) in the MB and 26 (20-33) in the TP groups. Median dose of NE at enrollment of the control, MB, and TP groups were 0.55 mcg/kg/min (0.52-0.58), 0.88 mcg/kg/min (0.81-1.00), and 0.66 mcg/kg/min (0.60-1.04), respectively. Survival rate at 7 days of control, MB, and TP group were 33.3%, 40.0%, and 50% respectively; p-value=0.84. Survival rate at 28 days were 16.7% in the control group, 40.0% in the MB group, and 16.7% in the TP group; p-value=0.59. From this pilot data, the calculated sample size to detect difference in survival rate at 28 days, with 5% significant level and 80% power, was 60 cases in each group. In survived cases, median time to wean off vasopressor of the control, MB, and TP groups were 3 days (2-4), 3 days (3-3), and 6 days (5-8); p-value=0.199. In survived cases, median time ICU duration of the control, MB, and TP groups were 19.5 days (6-33), 5 days (4-6) days, and 19 days (17-20), p-value=0.199. Peripheral gangrene was reported in 17.0% of the control, 33.3% of the TP group, but none in the MB group.

Conclusion: The difference in survival rate at 7 days and 28 days, as well as time to wean off vasopressor, and duration in ICU between the 3 groups are not detected due to small sample size. Further study is needed to determine the clinical effect of alternative vasopressors.

Keywords: Refractory septic shock, Terlipressin, Methylene blue, Septic shock