Prevalence and Long-Term Outcomes of Metformin-Associated Lactic Acidosis with Severe Acute Kidney Injury : an Ancillary Analysis of the SEA-AKI Study

P. Kaewdoungtien [a,b,c*], P. Kusirisin [a,b,c,d], S. Peerapornratana [a,b,c,f], N. Srisawat [a,b,c,e]

[a] Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;
[b] Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand;
[c] Critical Care Nephrology Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;
[d] Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand;
[e] Academy of Science, Royal Society of Thailand, Bangkok, Thailand
[f] Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Background and Objective

Metformin-associated lactic acidosis (MALA) is a serious emergent condition associated with increased morbidity and mortality. However, MALA is an unrecognized cause of severe acute kidney injury (AKI), especially in developing countries. We aimed to investigate the prevalence, clinical characteristics, and long-term outcomes of patients with MALA.

Method

We conducted a secondary analysis of the Southeast Asia-Acute Kidney Injury (SEA-AKI) study, an ongoing prospective study in 14 centers across Thailand between May 2019 and September 2021. Briefly, the SEA-AKI study enrolled critically ill patients with stage 3 AKI according to the Kidney Disease Improving Global Outcome (KDIGO) criteria to examine the long-term outcomes up to 24 months. Major Adverse Kidney Events at 30 days ($MAKE_{30}$) and 365 days ($MAKE_{365}$) defined by death, dialysis dependent, and doubling serum creatinine. In this analysis, we only examined the patients with history of metformin use concomitant with severe metabolic acidosis.

Results

Clinical data were obtained from 1,328 ICU patients with stage 3 AKI. Among these, 142 (10.7%) patients met the diagnostic criteria for MALA. These patients had more frequent history of dehydration, vomiting, diarrhea and exposure to nephrotoxic agents (Table 1).

	MALA N=142	Non-MALA N=1,216	p-value
Male, n (%)	73 (51.4)	749 (61.6)	0.060
Age, year	63±11	61±18	0.210
Clinical presentation, n (%)			
Dehydration	75 (52.8)	175 (14.4)	<0.005
Vomit	53 (37.3)	39 (3.2)	<0.005
Diarrhea	57 (40.1)	98 (8.1)	<0.005
Exposure of Nephrotoxic agent	20 (14.9)	51 (4.2)	<0.005
Laboratory data			
Creatinine, mg/dL	8.1 (3.6-11.1)	2.2 (1.3-4.1)	<0.005
Potassium, mEq/L	5.4 (4.7-6.4)	4.2 (3.7-5.0)	<0.005
Bicarbonate, mEq/L	6 (3.3-10)	16 (12-20)	<0.005
Hemoglobin, g/dL	10.1 (9.1-11.4)	9.8 (8.2-11.9)	0.850
Albumin, g/dL	3.4 (3.1-3.8)	2.8 (2.4-3.3)	<0.005
Kidney replacement therapy (KRT)			
Kidney replacement therapy, n (%)	108 (76.0)	757 (62.3)	<0.005
Duration of KRT in 1st week, day	1 (1-2)	2 (1-3)	<0.005
Day of KRT initiation from enrollment, day	1 (1-2)	4 (2-8)	<0.005
Modality, n (%)			
Intermittent hemodialysis	75 (52.8)	371(30.56)	<0.005
Slow low efficiency dialysis	5 (3.5)	114 (9.4)	0.020
Continuous kidney replacement therapy	19 (13.4)	305 (25.1)	<0.005
Peritoneal dialysis	22 (15.5)	77 (6.3)	<0.005
Mechanical ventilator, n (%)	103 (72.5)	836 (68.8)	0.570
Vasopressor, n (%)	94 (66.2)	725 (59.6)	0.130
SOFA score	9 (6-11)	10 (7-13)	<0.005
APACHEII score	21 (16-27)	23 (17-29)	0.200

Data shown as mean ± SD, or median(interquartile range).

Table 1. Baseline patient's characteristics

Compared to patients without MALA, those with MALA were associated with more severe azotemia, hyperkalemia, and metabolic acidosis. Rate of kidney replacement therapy (KRT) was also higher in MALA group (76.0% versus 62.3%, p=0.001). KRT initiation in MALA group was significantly earlier with shorter duration. Patients with MALA had significantly lower incidence of $MAKE_{30}$ and $MAKE_{365}$ than those without MALA (90% versus 95%, p = 0.038); and 62% versus 85%, p < 0.005); respectively). Cox-regression analysis showed a significantly lower mortality in MALA group up to 1 year (p < 0.001).

	MALA	Non-MALA	p-value
MAKE 30 days	90%	95%	0.038
Death	21%	50%	<0.001
Dialysis	91%	74%	<0.001
Doubling Serum Cr	34%	53%	<0.001
MAKE 365 days	62%	85%	<0.001
Death	60%	83%	<0.001
Dialysis	0%	10%	0.140
Doubling Serum Cr	20%	17%	0.860

Table 2. Composite outcomes

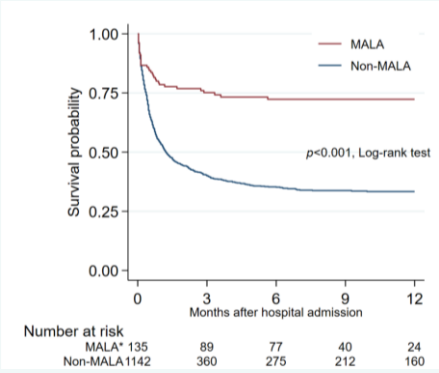

Figure 1. Kaplan-Meier Curve of time to death

Conclusion

MALA in developing world is not uncommon. Patients with MALA frequently had history of volume depletion and concomitant nephrotoxic exposure. Early recognition and KRT resulted in good short- and long-term outcomes. Metformin should be used with caution in high-risk patients.

Contact: e-mail: pynkdt@yahoo.com (PK); drnattachai@yahoo.com (NS)