DIURESIS EFFECTIVENESS OF AMINOPHYLLINE AND FUROSEMIDE COMBINATION IN CRITICALLY ILL ADULTS

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF ANAESTHESIOLOGY

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ABSTRACT

Furosemide is commonly used to improve urine output; however its use is not without complications. Aminophylline, a potent bronchodilator, has also been shown to exhibit diuretic properties though its effects on renal vascular. Concurrently use of Aminophylline and Furosemide has been used clinically in adult patients undergoing cardiac surgery and in paediatric population, especially in neonates. However, evidence of Aminophylline and Furosemide combination use in critically ill adults is scarce.

We conducted a randomised controlled trial in University of Malaya Medical Center intensive care unit from 1st July 2023 up to 31st March 2024, to compare the effectiveness of aminophylline and furosemide combination versus furosemide alone in producing effective diuresis. A total of 28 adult ICU patients were randomly divided into intervention group (n = 14) and control group (n = 14). The intervention group received infusion of Aminophylline 150mg and Furosemide 120mg diluted in 50ml normal saline, while control group received infusion of Furosemide 120mg diluted in 50ml normal saline. Primary outcome was diuresis effectiveness 6 hours post intervention, effective diuresis was defined as urine output > 0.5ml/kg/hr. Secondary outcomes include diuresis effectiveness 2 hours post intervention, mean duration to produce effective diuresis, mean change of urine output over 6 hours, mean change of serum creatinine level and eGFR over one day, and the need for renal replacement therapy during ICU stay.

Our study revealed that intervention group was not superior to control group in producing effective diuresis within 2 hours and 6 hours period, however this finding was not statistically significant. There was no clinical difference in time taken for either group to achieve effective diuresis. Urine output over 6 hours improved more for control group. There was less increase in serum creatinine level and less reduction in eGFR in intervention compared to control group. There were more patients who had RRT during their ICU stay in control group compared to intervention group.

In conclusion, the infusion of combined Aminophylline and Furosemide is not superior to Furosemide alone in producing effective diuresis. The combined infusion may have a renal protective effect, but our findings need to be confirmed by future study with larger sample size.

Keywords: Aminophylline, Furosemide, Diuretic, Critically Ill, Adults

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ABSTRAK

Furosemide biasanya digunakan untuk meningkatkan pengeluaran air kencing; namun penggunaannya tidak terlepas dari komplikasi. Aminophylline, sebatian bronkodilator yang kuat, juga telah terbukti sifat diuretiknya melalui kesannya pada vaskular buah pinggang. Penggunaan serentak Aminophylline dan Furosemide telah digunakan secara klinikal dalam kalangan pesakit dewasa yang menjalani pembedahan jantung dan juga dalam populasi pediatrik, terutamanya pada bayi baru lahir. Walau bagaimanapun, bukti penggunaan gabungan Aminophylline dan Furosemide dalam pesakit dewasa yang kritikal masih jarang.

Kami telah menjalankan ujian kawalan secara rawak di Unit Rawatan Rapi Pusat Perubatan Universiti Malaya dari 1 Julai 2023 hingga 31 Mac 2024, untuk membandingkan keberkesanan gabungan Aminophylline dan Furosemide berbanding Furosemide sahaja dalam menghasilkan diuresis yang berkesan. Sejumlah 28 pesakit dewasa ICU telah dibahagikan secara rawak kepada kumpulan intervensi (n = 14) dan kumpulan kawalan (n = 14). Kumpulan intervensi menerima infusi Aminophylline 150mg dan Furosemide 120mg yang dicairkan dalam 50ml larutan garam fisiologi, manakala kumpulan kawalan menerima infusi Furosemide 120mg yang dicairkan dalam 50ml larutan garam fisiologi. Hasil utama adalah keberkesanan diuresis 6 jam selepas intervensi, di mana diuresis yang berkesan ditakrifkan sebagai pengeluaran air kencing > 0.5ml/kg/jam. Hasil sekunder termasuk keberkesanan diuresis 2 jam selepas intervensi, purata tempoh untuk menghasilkan diuresis yang berkesan, purata perubahan

jumlah pengeluaran air kencing dalam tempoh 6 jam, purata perubahan paras serum kreatinin dan kadar eGFR sehari selepas intervasi, dan keperluan untuk terapi dialysis semasa penginapan ICU.

Kajian kami mendapati bahawa kumpulan intervensi tidak lebih unggul daripada kumpulan kawalan dalam menghasilkan diuresis yang berkesan dalam tempoh 2 jam dan 6 jam, namun dapatan ini tidak signifikan secara statistik. Tiada perbezaan klinikal dalam masa yang diambil oleh mana-mana kumpulan untuk mencapai diuresis yang berkesan. Pengeluaran air kencing dalam tempoh 6 jam lebih baik untuk kumpulan kawalan. Peningkatan paras kreatinin serum dan penurunan paras eGFR kurang dalam kumpulan intervensi berbanding kumpulan kawalan. Terdapat lebih banyak pesakit yang menjalani terapi dialysis semasa penginapan mereka di unit rawatan rapi dalam kumpulan kawalan berbanding kumpulan intervensi.

Secara kesimpulannya, infusi gabungan Aminophylline dan Furosemide tidak lebih unggul daripada Furosemide sahaja dalam menghasilkan diuresis yang berkesan. Infusi gabungan mungkin mempunyai kesan perlindungan terhadap buah pinggang, tetapi dapatan kami perlu disahkan oleh kajian masa depan dengan saiz sampel yang lebih besar.

Kata kunci: Aminofilin, Furosemide, Diuretik, Kritikal, Dewasa

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LIST OF SYMBOLS AND ABBREVIATIONS

CI	:	Confidence Interval
CKD	:	Chronic Kidney Disease
eGFR	:	Estimated Glomerular Filtration Rate
GFR	:	Glomerular Filtration Rate
ICU	:	Intensive Care Unit
RRT	:	Renal Replacement Therapy
UMMC	:	University of Malaya Medical Center

CHAPTER 1 GENERAL INTRODUCTION

In University Malaya Medical Center (UMMC) intensive care unit (ICU), patients with the need for diuresis are typically treated with intravenous (IV) infusion of Aminolasix. Aminolasix is a combination of Aminophylline 150mg and Furosemide 120mg in 50ml of normal saline. This setup will result in a solution of 3mg/ml Aminophylline and 2.4mg/ml Furosemide, which produces an infusion of 50mcg/ml/min Aminophylline and 40mcg/ml/min Furosemide. Infusions are typically ran at a rate of 4ml per hour, resulting in an infusion of 200mcg/min Aminophylline and 160mcg/min Furosemide.

Furosemide is a commonly used loop diuretic, however its use is not without risks. Furosemide carries a serious risk, namely ototoxicity, which may cause temporary or permanent hearing loss. The risk of ototoxicity is particular high when the plasma furosemide concentration exceeds 50mcg/ml(1).

Aminophylline, on the other hand, is an established bronchodilator, it is now known to also be a potent diuretic. Purposed mechanisms include type IV phosphodiesterase inhibition or adenosine receptor blockade.

In animal studies, concurrent administration of Aminophylline and Furosemide had resulted in an infra-additive response(2). Clinically, Aminophylline has been used concurrently with Furosemide to induce diuresis in adults undergoing cardiac surgery(3, 4) and in children(5-12), especially in neonates(13-21).

Recent systemic review has shown that the combined use of Aminophylline/Theophylline and Furosemide potentially yield better diuretic effects of urine output and negative balance than Furosemide alone in fluid overloaded paediatric patients(22). However, evidence on the use of Aminophylline in adult critical care patients is scarce.

We aim to study whether the infusion combination of Aminophylline and Furosemide is superior compared to infusion of Furosemide alone in producing effective diuresis in critically ill adults in ICU.

CHAPTER 2 LITERATURE REVIEW

A systemic review by Van Siang Liang Mang et al in 2022, shown that the combined use of Aminophylline/Theophylline and Furosemide potentially yield better diuretic effects of urine output and negative balance than Furosemide alone in fluid overloaded paediatric patients. Their data showed combined use of Aminophylline/Theophylline and Furosemide associated with high urine output increase as compared to furosemide alone. However, the sample size was only a mere 187 patients, pooled from five different. They study was further limited by stark variability from broad pediatric age groups ranges with different regimes dosages and duration across included studies(22).

In 2012, da Silva et al reported a prospective case series of four critically ill children unresponsive to furosemide continuous infusion who were given aminophylline as an adjunct diuretic in the treatment of fluid overload. The use of Aminophylline at low doses (3 mg/kg) managed to increase urine output over the 6 hours study period in all four children. The mean urine output increase was 275% at 2 hours after intervention and 195% at 6 hours after intervention(8).

In a 2016 RCT, Onder et al compared Aminophylline and Furosemide to treat intraoperative oliguria in 200 children with congenital heart disease in pediatric intensive care unit (PICU), found that Aminophylline increases urine output and reduces the need for renal replacement therapy compared to furosemide in pediatric populations post cardiac surgery(11).

In 1990, Noguchi et al studied the effect of aminophylline in 11 adult patients after cardiac surgery. They administered Aminophylline at 2ml/kg/hr when urine output

dropped to less than 1ml/kg/hr. The results showed Aminophylline increased urine output by 70%, and suggested that it is secondary to the increase in renal blood flow(4).

In a 2017 double blind, randomised placebo controlled trial, Shahbazi et al studied the effect of Aminophylline in reducing the incidence of acute kidney injury in 144 adults post cardiac surgery. The intervention group was given a bolus of 5 mg/kg Aminophylline prior to surgery and after induction of anaesthesia; followed by, 0.25 mg/kg/hour Aminophylline intraoperatively and up to 48 hours post surgery in the cardiac ICU. Postoperative urine output were not significantly different between the two groups. Based on significant improvements to GFR and creatinine levels, they concluded that Aminophylline can reduce the incidence of acute kidney injury and is safe and efficient in high-risk cardiac surgery patients(3).

There was no reports on the use of combined infusion of Aminophylline and Furosemide in adult ICU patients. Adult studies centered on cardiac surgery patients. Most studies in paediatric ICU population has very small sample size, and it is difficult to extrapolate their findings to our population. Overall, the literature pointed that the addition of Aminophylline on top of Furosemide would yield better urine output in certain population, with some suggestion of potential renal protective effect from Aminophylline use.

CHAPTER 3 METHODOLOGY

3.1 Hypothesis

IV infusion of Aminophylline and Furosemide combination is more effective in producing diuresis in adult ICU patients, compared to IV Furosemide infusion alone.

3.2 Objectives

3.2.1 Primary Objective

To compare the effectiveness of aminophylline and furosemide combination versus furosemide alone in producing effective diuresis, 6 hours post intervention. (Effective diuresis is defined as urine output >0.5ml/kg/hr)

3.2.2 Secondary Objectives

1. To compare the effectiveness of aminophylline and furosemide combination versus furosemide alone in producing effective diuresis, 2 hours post intervention.

2. To compare the mean duration of infusion to achieve effective diuresis between intervention groups.

3. To compare the changes in serum creatinine, eGFR, and urine output over time between intervention groups.

4. To compare the need for Renal Replacement Therapy (RRT) between intervention groups during ICU stay.

3.3 Study Location

The study was conducted in the adult Intensive Care of University of Malaya Medical Centre (UMMC), which is a mixed medical and surgical ICU.

3.4 Study Period

The study was conducted over a 9 months period, from 1st July 2023 up to 31st March 2024.

3.5 Study Design

The study was conducted as a double blind, randomised, controlled trial.

3.6 Study Population

3.6.1 Inclusion Criteria

1. Patients aged 18 years old and above who are admitted to the ICU of UMMC during the study period.

2. Patients with the need for improved diuresis at clinician discretion.

3.6.2 Exclusion Criteria

1. Patient or next of kin's refusal for participation of study.

2. Patient with known hypersensitivity reaction to Aminophylline or Furosemide

3. Patient with history of tachyarrhythmias, seizures, aspartate aminotransferase or alanine aminotransferase > 3 times normal, or hypothyroidism.

4. Patient with existing peptic ulcer disease or coagulopathy with international normalized ratio (INR) of more than 1.5

3.7 Sampling Method

All patients who were admitted to the adult ICU of UMMC during the study period, and required intravenous infusion of diuretics during ICU stay were screened for eligibility and were recruited for the study.

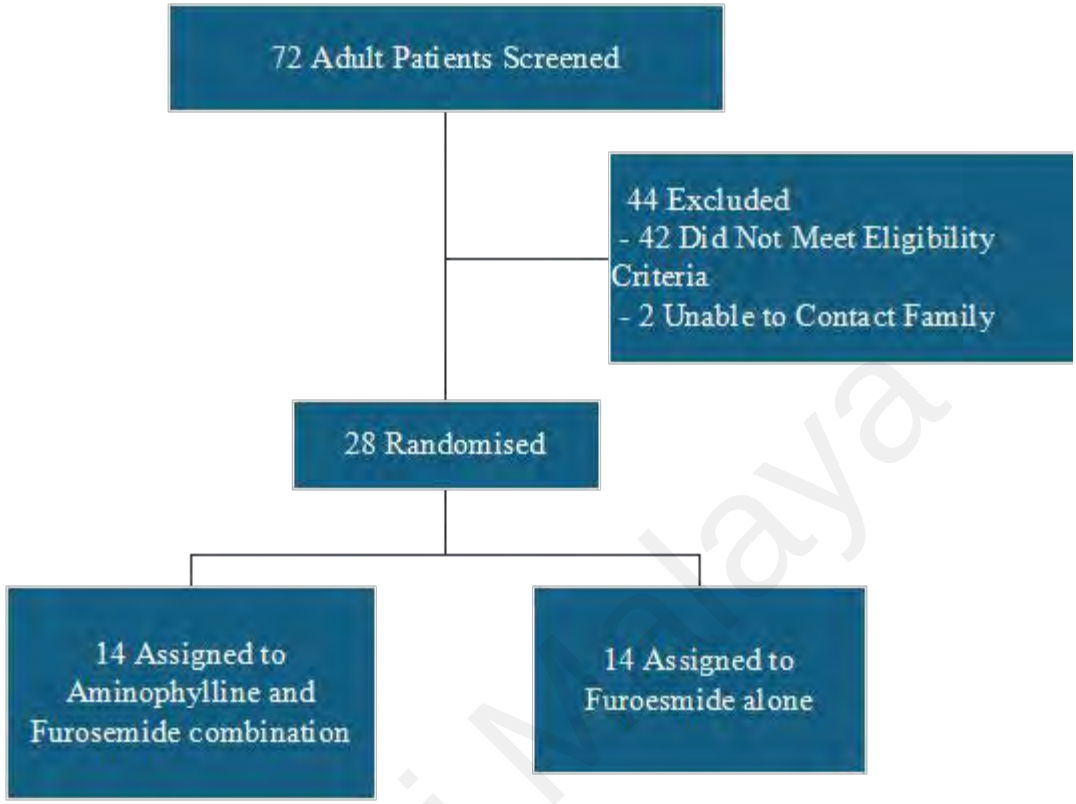
3.8 Sample Size

Sample size calculation was done using OpenEpi software. Under assumptions of 50% of control group and 75% of intervention group would achieve effective diuresis, we would need a sample size of 116 (58 in each group) to achieve power of 0.8 and a level of significance of 5%, for declaring that the combination drug is superior to control drug. Accounting for potential dropout of 10%, we needed a final sample size of 132 (66 in each group.

3.9 Randomisation

Recruited patients were randomised using stratified block randomization for patients with or without chronic kidney disease (CKD), into intervention group or control group/ Two sets of sequentially numbered, opaque, sealed envelopes were prepared for patient with or without CKD.

Figure 3.1: Flowchart of Trial Patients



3.10 Intervention

3.10.1 Intervention Group

Patient were given IV infusion of Aminolasix (Aminophylline 150mg and Furosemide 120mg diluted to 50ml of normal saline), IV load 10ml over 60 minutes, followed by IV infusion of 4 ml/hour

3.10.2 Control Group

Patient were given IV infusion of Furosemide (Furosemide 120mg diluted to 50ml of normal saline), IV load 10ml over 60 minutes, followed by IV infusion of 4 ml/hour

In both groups, clinicians were free to titrate the infusion rate according to patient's clinical response. Intervention were stopped at clinician discretion once effective diuresis was achieved or if patient's haemodynamic was compromised.

In the event of newly developed tachyarrhythmias, clinicians were able to stop the infusion of study drug. And if diuretic infusion was still indicated, the choice of open label Furosemide infusion was used instead.

3.11 Ethics

The study was reviewed and was approved by the Medical Research Ethics Committee (MREC) of UMMC. (MREC ID NO: 202334-12198)

The study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from the patients or their next of kin.

3.12 Data Collection

Baseline patient data were included as concomitant study parameters. Relevant patient and clinical data included basic demographic information (age, gender, and ethnicity), body weight, known underlying chronic kidney diseases, previous diuretics administration prior to intervention, urine output, serum creatinine level, serum eGFR, the need for RRT during ICU stay and any complications such as tachyarrhythmias. These information were collected using a data collection sheet, and managed in a confidential manner.

3.13 Data Analysis

Data analysis was done using the SPSS Software version 20. Descriptive analysis were expressed as percentages and mean/median, whichever appropriate. Categorical variables were expressed as percentages and compared using the Chi-square. Continuous variables were expressed as mean and compared using unpaired t-test. In all instances, p-value of less than or equal to 0.05 were considered to be significant.

CHAPTER 4 RESULTS

Table 4.1 Baseline Demographics

Variable	Intervention Group (n = 14)	Control Group (n = 14)
Sex		
Male	6 (42.8%)	9 (64.2%)
Female	8 (57.2%)	5 (35.8%)
Age (years)	56.50 ± 13.7	60.43 ± 15.52
Weight (kg)	67.69 ± 17.86	75.72 ± 18.47
Ethnicity		
Malay	3 (21.4%)	6 (42.8%)
Chinese	4 (28.6%)	4 (28.6%)
Indian	6 (42.8%)	4 (28.6%)
Others	1 (7.2%)	0
Comorbidities		
Diabetes Mellitus	7 (50%)	9 (64.2%)
Hypertension	9 (64.2%)	8 (57.2%)
Ischemic Heart Disease	3 (21.4%)	3 (21.4%)
Chronic Kidney Disease	4 (28.6%)	5 (35.8%)
Urine output at start (ml/kg/hr)	0.32 ± 0.32	0.41 ± 0.55
Non-oliguria at start	2 (14.3%)	5 (35.8%)
Use of diuretics prior to recruitment	4 (28.6%)	7 (50%)
Total dosage of diuretics given prior to recruitment	0.19 ± 0.38	0.23 ± 1.21

Serum creatinine at start (mcmol/L)	247.71 ± 206.62	197.14 ± 124.47
eGFR at start	36.93 ± 26.11	40.64 ± 26.13
RRT prior to recruitment	2 (14.3%)	5 (34.8%)

The baseline demographics of adult ICU patients are shown in Table 4.1. There were no significant differences in age and weight between the groups. There were 20% more male seen in control group. There were also more Indian patients compared to Malay patients seen in intervention group. These observations are not reflective of our Malaysian general population and are likely due to the same sample size analysed.

Both groups have comparable comorbidities, including underlying chronic kidney disease. The baseline urine output at the beginning is higher in the control group. As patients were included in the study when the clinicians felt the need to improve diuresis, not all recruited patients were oliguric. This appeared to be more prevalent in the control group, in which 35.8% of them were not oliguric to begin with compared to 14.1% in the intervention group.

We also captured whether the recruited patients were given any diuretics prior to recruitment. Half of the control group were given diuretics before while 28.6% of intervention group were given diuretics. In both cases, the diuretics given were IV Furosemide, and the dosage given noted was comparable.

In terms of laboratory investigations, both groups have comparable level of serum creatinine and eGFR upon recruitment. Although we wanted to study whether our intervention influenced the need of RRT for patients during their ICU stay, we noticed 14.3% of intervention group and 34.8% of control group had RRT prior to recruitment into our study.

Table 4.2 Outcomes

Outcome	Intervention Group (n = 14)	Control Group (n = 14)	p-Value
Effective diuresis within 6 hours of infusion	7 (50%)	11 (78.6%)	0.115
Effective diuresis within 2 hours of infusion	6 (41.8%)	9 (64.2%)	0.256
Duration needed to achieve effective diuresis (hours)	1.57 ± 0.79 (n = 7)	2.00 ± 1.55 (n = 11)	0.304
Urine output increase over 6 hours intervention (ml/kg/hr)	0.56 ± 0.81	± 0.67 ± 0.91	0.628
Serum creatinine changes 1 day post intervention	30.43 ± 101.86	52.5 ± 42.77	0.200
eGFR changes 1 day post intervention	-3.78 ± 9.66	-9.21 ± 8.28	0.919
RRT during ICU stay	7 (50%)	10 (71.4%)	0.246

The primary outcome revealed that intervention group was not superior to control group in producing effective diuresis within 6 hours period, 50% compared to 78.6% respectively, however this finding was not statistically significant with a p-value of 0.115.

Similarly, secondary outcomes showed that intervention group did not perform better within 2 hours period, 41.8% compared to 64.2% respectively. There was no clinical difference in time taken for either group to achieve effective diuresis. Urine output over 6 hours improved more for the control group, however this was not statistically significant either. There was less increase in serum creatinine level and less reduction in eGFR in intervention compared to control group. There were more patients who had RRT during their ICU stay in control group compared to intervention group, 71.4% and 50% respectively.

CHAPTER 5 DISCUSSION

In this randomized controlled trial, infusion of Furosemide alone was more effective in producing effective diuresis compared to the combination of Aminophylline and Furosemide. This was shown by infusion of Furosemide alone performed better at producing effective diuresis at 2 and 6 hours post intervention, and higher mean urine output increase over 6 hours. This finding, however, was not statistically significant and was limited by the small sample size due to the low recruitment rate.

On the other hand, the combined use of Aminophylline and Furosemide infusion appeared to be more renal protective, showing less increase in serum creatinine level, lower reduction in eGFR and lower need for renal replacement therapy during their ICU stay. However, we need to be cautious when interpreting these results as it is also statistically not significant and more patients in the control group already had RRT prior to recruitment.

Our current finding supports the theory that Furosemide can increase the patients' urine output, but it does not improve the renal function(23, 24). The addition of Aminophylline could potentially have a renal protective effect as shown by systemic review and meta-analysis on its use in pediatric population(25). A recent randomized placebo-controlled trial studied the use of low-dose Furosemide combined with Aminophylline in septic shock patients, the infusion over 7 days improved urine output, SOFA score, hospital and 28 days mortality, but showed no improvement in renal function(26).

Out of our 28 study participants, a patient developed fast atrial fibrillation while the patient was on study drug infusion. The patient was treated with medical therapy and the clinician in charge stopped and changed the study drug to open label Furosemide infusion. It was later revealed that the patient was in the control group after interventions were unblinded for data analysis.

Our study had certain limitations. The abysmal recruitment rate in our study was mainly attributed to our exclusion criteria of liver derangement and coagulopathy, which were common in ICU patients with multiorgan involvement. Among our 77 screened patients, 22 of them had liver derangement while 15 of them had coagulopathy. Our small sample size caused our mean outcome to be easily skewed by outliers. There may have been multiple confounding variables, such as diuretic resistance, particularly patients on long term diuretics. Furthermore, our study did not take into account the concurrent use of nephrotoxic drugs, antibiotics and inotropes.

Lastly, the strength of our study lies in pioneering the study of the combined use of Aminophylline and Furosemide in critically ill adult population, it can serve as a good pilot study in designing future study with larger sample size.

CHAPTER 6 CONCLUSION

In summary, the combination of Aminophylline and Furosemide infusion is not superior to Furosemide alone in producing effective diuresis. The combined infusion may have a renal protective effect, but our findings need to be confirmed by future study with larger sample size.

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