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Multi-centre retrospective observational study: Length of stay, mortality and intubation ratio of patients diagnosed with hypertensive cardiogenic pulmonary edema managed with high dose furosemide vs high dose nitroglycerin for the first two hours

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ABSTRACT

Aims: The purpose of this study is to evaluate the length of stay of patients admitted with diagnosis of hypertensive cardiogenic pulmonary edema (HCPE) when managed with furosemide vs high nitroglycerin as monotherapy. Other outcomes such as: mortality during admission and orotracheal intubation will be evaluated as well. Methods: Retrospective observational multi-center study composed of 137 patients, performed reviewing medical records from January-2016 to January-2018 at San Juan Hospital and Aibonito's Hospital. We analyzed data from patients admitted with diagnosis of HCPE, classified in two groups: nitroglycerin and furosemide. Our primary outcome was to evaluate the length of stay. Results: The nitroglycerin group reported a length of stay of 4.89 days, orotracheal intubation rate of 6% and a mortality rate of 3%. The high dose furosemide was remarkable for a length of stay of 9.88 days, orotracheal intubation 18% and mortality rate of 9%. Conclusion: Physicians are accustomed to managing this disease with high dose diuretics, which is pharmacologically and physiologically counterproductive, despite of several studies demonstrating the benefit of high dose nitroglycerin. Medical literature should emphasize in the newer management of HCPE.

Keywords: Furosemide, Heart failure, Nitroglycerin, Pulmonary edema

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INTRODUCTION

HCPE is a hyperacute complication of congestive heart failure (CHF) and is defined as the accumulation of fluid in the lung secondary to an abrupt increase of hydrostatic pressure, which causes extravasation of fluid from the lung circulation into the interstitium [1]. HCPE should not be confound with acute decompensated heart failure, where the former presents with severe symptoms manifested as tachypnea, hypertension, breathing difficulty and hypoxemia that can lead to an imminent acute respiratory failure, whereas in acute decompensated heart failure patient presents with a more gradual onset of symptoms.

HPCE has an incidence of 10/1000 and poses a high prevalence of over 5 million patients in the United States, which represents over 1,000,000 of admissions annually [2–4]. It is stipulated that patients with HCPE represents 25% of CHF admissions, in other words, HCPE represents over 250,000 admissions in the United States with a high mortality that range from 15%-20% [5–6]. Special attention should be paid to elderly population, in view that median age for acute pulmonary edema is 74 years [7]. Patients overall, presents with multiples comorbidities where the most commons are: elevated blood pressure and coronary artery disease [8].

HCPE is defined as the accumulation of fluid in the lung secondary to an abrupt increase of hydrostatic pressure, which cause extravasation of fluid from the lung circulation into the alveolar space and interstitium, built up as transudate, as explained by the Starling relationship formula [9]. The normal pulmonary capillary wedge pressure (PCWP) ranges from 8-12 mm Hg and colloid oncotic pressure is 25 mm Hg [10–11]. The cardiac output will be reduced due to the left atrial impairment or left ventricle dysfunction, which transmit the pressure backwards to the pulmonary capillaries, therefore the PCWP will increase exceeding the oncotic pressure and accumulating fluid resulting in pulmonary edema, overt hypoxia and hindering gas exchange. The cardiac output will not supply the metabolic needs, increasing the catecholamines which at the same time increase the systemic vascular resistance and blood pressure with further increase in the end-diastolic pressure with concomitant continue elevation of PCWP (Figure 1).

HCPE can be triggered by the following etiologies: acute exacerbation of left ventricular dysfunction, cardiac ischemia, severe elevated blood pressure, aortic and/or mitral valve dysfunction and acute dysrhythmias. Must be noticed that fluid overload is not mentioned as an etiologic cause, although patients with HCPE have increased filling pressure, only 50% patients had minimal weight gain and were not fluid overloaded [12–13].

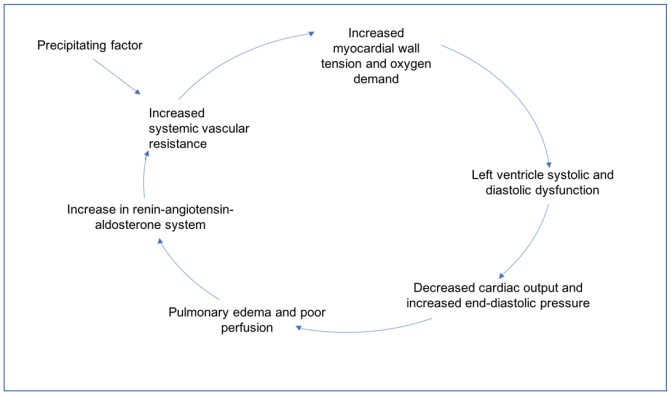

Figure 1: Summary of HCPE physiopathology.

However, regardless the etiologic origin, it will trigger the aforementioned cycle, whom must be handled from the base (preload and after load) at the same time. During the last decades, the management of HCPE has suffered several transformations and there is no established guideline for the management of HCPE. Furosemide has been the cornerstone management for this pathology, however, literature has advocated in favor of high dose nitroglycerin, augmenting better outcomes and reduced length of stay and orotracheal intubation ratio.

We conducted this retrospective observational study to compare the length of stay, orotracheal intubation risk and mortality rate in Hispanics patients diagnosed with HCPE managed with high dose furosemide and high dose nitroglycerin. Based on previous analysis, our hypothesis is that patients managed with high dose nitroglycerin by the first encounter physician can decrease the length of stay and decrease the risk for orotracheal intubation. This management could redound in a decrease of cost in this high prevalent disease.

MATERIAL AND METHODS

This retrospective observational multi-center study was performed reviewing medical records after Institutional Review Board approval by the San Juan City Hospital. Although recent studies had shown the superiority of nitroglycerin; however, they were performed in combination with other drugs. Hence, we performed a retrospective analysis of medical records from January 2016 to January 2018 at San Juan City Hospital and Aibonito's General Hospital. We analyzed data from patients admitted at the hospital with primary diagnosis of hypertensive cardiogenic pulmonary edema and patients were classified in two groups: high dose nitroglycerin and high dose furosemide, managed as monotherapy for the first 2 hours (head to head comparison). Blood pressure cut off to be included was greater than 150/90. Patients managed with multiple

drugs by the first encounter physician, end stage renal disease on hemodialysis, ST elevation myocardial infarction, non-ST elevation myocardial infarction and patients younger than 21 years were excluded. The data from both groups was collected to analyze our primary outcome: the length of stay and secondary outcomes: ratioof orotracheal intubation and mortality rate.

To obtain a power of >80%, the recommended sample size was 378, however, we analyzed 408 medical records that were admitted with the aforementioned diagnosis, but only 137 met the inclusion criteria, this sample size will lead to a margin error of 8.37%. In our study, we provide clinical information about sex distribution, New York Heart Classification, mortality rate, intubation rate and length of stay of patients admitted with diagnosis of hypertensive cardiogenic pulmonary edema at San Juan City Hospital and Aibonito's General Hospital.

RESULTS

The study was composed of 137 patients, where 95% of patients corresponded from a low-income base and 100% of patients where Hispanics (Caribbean region).

The nitroglycerin group was composed of 71 patients whereas the furosemide group was composed of 66 patients. The average age for the nitroglycerin group was 73 years while the average age for the furosemide group was 63 years, being analyzed with the Gauss bell chart. Sex distribution was remarkable for 79 male patients and 58 female patients. Comorbidities that were found to be equally distributed in both groups: hypertension, diabetes mellitus, chronic kidney disease and chronic obstructive disease. Average systolic blood pressure was 172 mmHg for nitroglycerin group and 178 mmHg for the furosemide group and the average diastolic blood pressure was 99 mmHg for the nitroglycerin group and 99 mmHg or the furosemide group. In addition to the epidemiologic data, patients were classified as their functional status prior to admission using the New York Heart Classification. The high dose nitroglycerin group reported a length of stay of 4.89 days, orotracheal intubation rate of 6% and a mortality rate of 3%. The high dose furosemide was remarkable for a length of stay of 9.88 days, orotracheal intubation 18% and mortality rate of 9%.

DISCUSSION

The most common causes of heart failure exacerbations are: forgot medications, symptomatic anemia, arrhythmias, ischemia, life style modifications, cardiac output upregulation, renal failure and pulmonary embolism. This pathology is one of the most fearful conditions presented at the emergency room, where patients are severely desperate, and physicians need to start management practically based on medical history, physical examination and chest X-ray. Unfortunately, those findings pose a sensitivity that is not superior to 70% [13]. Classic physical findings for hypertensive cardiogenic pulmonary edema are: crackles, jugular venous distention, severe acute dyspnea (air hunger) and elevated blood pressure, thus patients need to be managed expeditiously. Furosemide has been considered the cornerstone in the management of hypertensive cardiogenic pulmonary edema, however, we must remark that base on our study patients managed with furosemide, presented a length of stay of 9.9 days, intubation rate of 18% and mortality rate of 9% (Chart 1–3). Nowadays, this drug has been replaced by other drugs, currently, physicians pose a broad pharmacologic arsenal against this HCPE, but only few drugs have no dose modification and gather the necessary pharmacologic characteristic to be considered the cornerstone and almost the standard of care. Those drugs should pose a rapid onset, titratable dose based on patient response, predictable effect, short half-life and a mechanism of action that block several pathways in the pathophysiology of this disease and must be recalled that during the acute phase of HCPE the organism augments the compensatory mechanism: activation of the renin-angiotensin-aldosterone system (RAAS), increase in the myocardial contractility and adrenergic system. Data was analyzed with T-test, where nitroglycerin vs furosemide showed the following values: nitroglycerin group presented a rate of intubation of 6% (p value: 0.003) vs 18% in the furosemide group (p value:

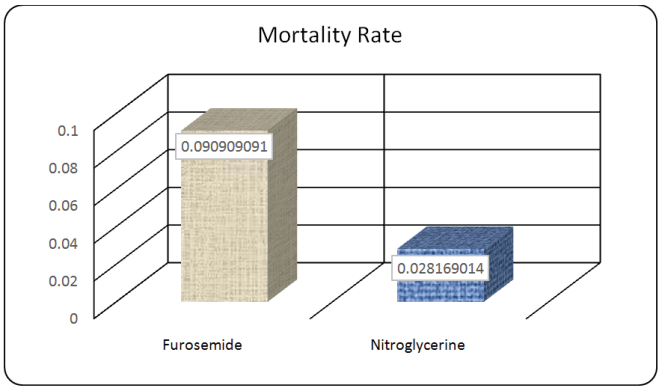

Chart 1: Mortality Rate.

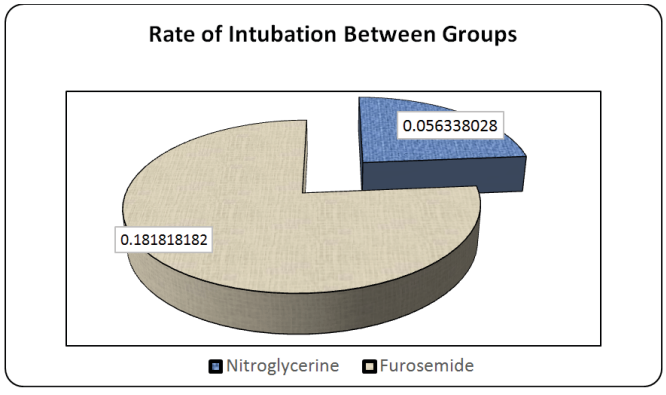

Chart 2: Intubation Rate.

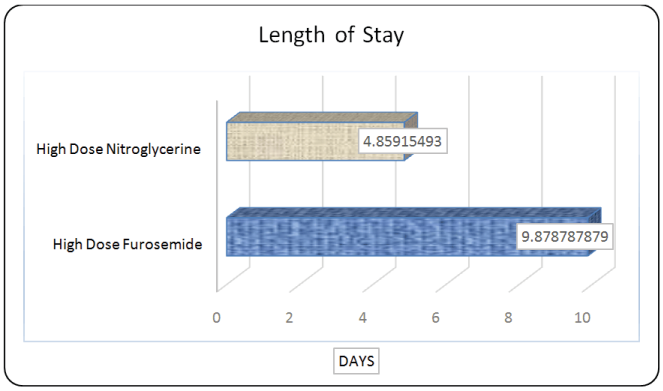

Chart 3: Length of Stay.

0.003), mortality rate of 3% vs 9% in the furosemide group (p value: 0.002) and length of stay of 4.9 days (p value: <0.003) vs 9.88 days in the furosemide group (p value: < 0.003) (Table 1). Our findings were similar to recent studies in regard to this pathology, showing the superiority of nitroglycerin over furosemide when managing HCPE. Nonetheless, recent studies were performed in combination with several drugs, as oppose to our study, nitroglycerin and furosemide were evaluated as monotherapy (head to hear comparison). To understand why those two groups, show a statistically significant difference we will describe the mechanism of action of either drug. Nevertheless, other drugs, not considered in this study, that are used for HCPE will be reviewed as well.

Preload

Otto Frank and Ernest Starling can be considered the pioneers in the cardiac physiology theme, where they first described the relationship between the end-diastolic volume and ventricular performance. The end-diastolic volume, also known as the preload, can be defined as the filling pressure of the heart at end of the diastole, which is intrinsically related to the myocardial distention and must not be confused with venous return [14]. To understand venous return, cardiac output must be understood first. Cardiac output is defined as the quantity of blood pumped by the heart for 60 seconds, similarly venous return is described as the quantity of blood returned to the heart [15]. Under normal physiology, the venous return must equal the cardiac output. The preload can be accessed from left ventricle end diastolic pressure with invasive and non-invasive studies, nevertheless, this approach is not necessary for the initial treatment [16]. As soon as the end diastolic volume increases, the stroke volume increases parallel trying to compensate. Conversely, a heart with a known disease, who received an augmented preload is unable to increment the stroke volume, resulting in a retrograde increased lung hydrostatic pressure. The first step in management should be to reduce the preload, thus subsequently, there will be decrease in the hydrostatic pressure.

Table 1: Showing P-values outcome comparison between nitroglycerin group and furosemide group in regard to: rate of intubation, mortality rate and rate of intubation

Outcome	Nitroglycerin group	Furosemide group	P-value
Rate of intubation	6%	18%	0.003
Mortality rate	3%	9%	0.002
Lenght of stay (days)	4.9	9.8	0.003

Nitroglycerin, known for its vasodilator effect, act donating nitric oxide with subsequent activation of guanylate cyclase in the vascular smooth muscle, resulting in dephosphorylation of myosin light chain. The final result is a marked vasodilator effect on the venous circulation and mild vasodilator effect on arteries with higher doses [17]. This effect results in an increased venous capacitance, causing a diminished venous return, which entails a decreased preload.

Nitroglycerin is presented in several formulations: translingual spray, sublingual tables transdermal patch, intravenous (IV) and topical. The topical and transdermal formulation pose an erratic absorption, thus are not recommended for HCPE management. Nitroglycerin IV, as described by its pharmacodynamics, pose an immediate onset with a rapid peak effect, and a short half-life, which range from 1-4 minutes (Chart 4) [18]. Nitroglycerin described as effective, titratable and safe drug for HPCE [19]. There are numerous head to head trials between nitroglycerin, furosemide and morphine in regard HCPE, where nitroglycerin was superior [20]. The superiority of nitroglycerin is due to his characteristics described previously (rapid onset, rapid peak and short half-life), even if hypotension is developed, stopping the drug for several minutes will suffice. Dose for HCPE is not the same as prescribed for chest pain or uncomplicated heart failure. For this pathology the recommended dosage is to be started at 20 mcg/min followed with increments of 15-20 mcg/min every 3 minutes for a maximum dose of 400 mcg/min [21-22]. When an infusion pump is not available, this drug can be prescribed as 3 mg IV bolus every 5 minutes, must be recalled that 3 mg is equivalent

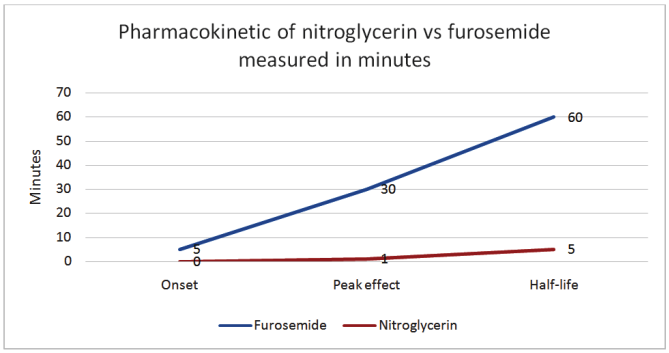

Chart 4: Furosemide vs Nitroglycerin pharmacokinetic measure in minutes.

to 600 mcg/ min [23]. Physicians are accustomed the ordinary antianginal sublingual nitroglycerine 0.4 mg dose which is equivalent to ~80 mcg/min IV.

Furosemide

Furosemide is a potent diuretic, loop diuretic, which blocks sodium and chloride reabsorption in the ascending loop of Henle, resulting in decrease preload. This diuretic is presented in several formulations: oral tablets and solution for intramuscular and intravenous use. Although it poses antihypertensive properties, the Eight Joint National Committee (JNC 8) does not recommend this drug for blood pressure management [24]. Currently, the indicated use of furosemide is for edema related to: kidney disease, heart disease, liver disease and pulmonary edema.

Furosemide mechanism of action is promising, however, when managing HCPE its own pharmacokinetics justify why it should be avoided as a monotherapy. Furosemide IV pose an onset of action of 5 minutes, with a delayed peak effect 30 minutes and a relative long half-life (60 minutes), when compared with nitroglycerin [25]. Whether furosemide is selected for the HCPE management, doses are elevated, ranging from 40-80 mg IV as bolus, with the considering rebolus in 20 minutes if no improvement [26]. Higher doses are associated to clinical improvement. However, it is associated with declination of glomerular filtration rate and augmented admission rate to intensive care units [27]. 50% of patients admitted with hypertensive cardiogenic pulmonary edema are euvolemic, thus high dose furosemide will result in a detrimental renal function. Furthermore, HCPE is described as a sympathetic and adrenergic state with augmented peripheral resistance, thus glomerular filtration rate will be overwhelmed already due to renovascular constriction [28]. As result of the previously mentioned stipulation, the peak effect will be considerable retarded, up to 45-120 minutes [29]. There are several studies that indicate that the prescription of furosemide for the initial stage of HCPE leads to counterproductive effect due to increment of the renal angiotensin aldosterone system (RAAS), which is a physiologic response to the volume contraction with final increase of the mean arterial pressure, vascular resistance and pulmonary capillary wedge pressure and a transitory decrease of the stroke volume [30].

Although our gathered data was statistically significant, because the p values were <0.05, however, our study was limited in several ways, the margin error was >5% and the sample size could not reach the power of 80%, hence, further multi-center studies with adequate power should be performed. Another limitation was most patients were not followed farther than one month, on future studies would be of benefit follow up patient for a longer time. Nevertheless, based in our study, the hospitalization cost of patients in the furosemide group was 106% more expensive than the hospitalization cost of patients in the nitroglycerin group, based on length of stay analysis.

When prescribing furosemide in HCPE, physicians must weigh the cardiovascular effects of this drug during HCPE (sympathetic and hyper-adrenergic state), but whether the use cannot be precluded (due to fluid overload state), we recommend premedication with nitroglycerin and ACE-inhibitor and prescribe furosemide later, once the clinical stability has been achieved, this strategy can blunt the cardiovascular and renal adverse effect of furosemide.

Unfortunately, cardiology associations and emergency medicine associations have not developed guidelines for the management of HCPE and the current management is based on recommendations with no guidelines to follow. This multi-center, retrospective, observational study can serve to evidence that high dose nitroglycerin is a safe and cost effective. As previously mentioned, there is enough evidence and controlled trials worldwide that will support the development of formal guidelines for the management of this pathology.

CONCLUSION

Physicians pose a great variety of drugs against HCPE, but only a few poses the pharmacokinetic characteristics that deserve their use managing this dire pathology. Several decades ago, furosemide was considered the cornerstone in the management of HCPE, but nowadays there is enough evidence that shows the superiority of intravenous nitroglycerin (pharmacokinetically and pharmacodynamically) when prescribed for HCPE, but unfortunately most physicians are reluctant to prescribe high dose nitroglycerin (over 100 mcg/min) and are still attached to the use of high dose furosemide despite of evidence of increased ratio of intensive care unit admission, increased ratio of tracheal intubation (mechanical ventilation) and high risk of acute kidney injury. The persistent prescription of furosemide could be cultural and customs, nevertheless, nitroglycerin high dose could be considered a cost-effective therapy in view of evidence of our study, that this aggressive medication can preclude tracheal intubation, do not affect renal function, do not increase intensive care unit admission as occur with furosemide.

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Conflict of Interest
Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.