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THE EFFECTS OF VASOPRESSORS ON GASTRIC INTRAMUCOSAL PH AND GASTRIC MUCOSAL – ARTERIAL CARBON DIOXIDE PARTIAL PRESSURE DIFFERENCE IN SEPTIC SHOCK

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ABSTRACT

Background & Aim: Splanchnic ischemia has been implicated in the pathogenesis of sepsis and is postulated to be an important factor in the development of multi-organ failure, and resultant mortality in critically ill patients. The aim of this study was to assess the effect of vasoconstrictors on the gastric intra-mucosal pH (pHi) and difference in the gastric mucosal and arterial carbon dioxide tension (PgCO2-PaCO2 gap) in patients with septic shock using gastric tonometry.

Material & Methods: The effect of hemodynamic drug infusions on the splanchnic circulation was determined in this study by the measurement of pHi and the PgCO2-PaCO2 gap. Fifty patients diagnosed with septic shock and treated with vasopressors were subjected to six- hourly recordings of pHi and the PgCO2- PaCO2 gap using gastric tonometery and arterial blood gas analysis over a 24-hour period. Statistical analysis was undertaken to identify the vasopressor/ combination which has the least as well as the maximum deleterious effect on pHi and the PgCO2 - PaCO2 gap. A low pHi and a rising PgCO2-PaCO2 gap were indicative of inadequate tissue perfusion resulting in splanchnic ischemia.

Result: Patients treated with norepinephrine or a combination of dobutamine and norepinephrine were found to have significantly higher mean pHi ($p<0.001$) values and lower mean PgCO2-PaCO2 gaps ($p<0.001$) within the specified time intervals. The mean pHi values were significantly decreased for three consecutive 6-hourly readings in the dopamine group. The PgCO2 - PaCO2 gap significantly widened over 12 hours of dopamine use but was not significantly higher than baseline at 18-hours post-initiation of the infusion. However, the mean pHi values at T1, T2 and T3 intervals were found to be significantly decreased in patients in the dopamine group in this study. Those receiving low - dose vasopressin exhibited significantly lower mean pHi values and widening of the PgCO2-PaCO2 gap ($p<0.05$). The use of epinephrine significantly increased the pHi at the third time interval and widened the PgCO2- PaCO2 difference.

Conclusion: In this study, norepinephrine and dobutamine in combination with norepinephrine were found to exert a protective effect on the splanchnic circulation by improvement in splanchnic perfusion as manifested be an improving pHi and a decreasing PgCO2 - PaCO2 gap in patients with septic shock. The overall effect of dopamine on the splanchnic circulation could not be unequivocally established in this study. Low - dose vasopressin exacerbated gastric intramucosal acidosis and increased the PgCO2-PaCO2 gap and thereby exerted a deleterious effect on the splanchnic circulation. The use of epinephrine (>18 hours) caused splanchnic ischemia demonstrated by a decreased pHi and a progressively widened PgCO2-PaCO2 gap.

KEYWORDS : Gastric intramucosal pH (pHi), gastric mucosal – arterial carbon dioxide partial pressure difference (PgCO2-PaCO2 gap) , splanchnic ischemia, septic shock, vasopressors.

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INTRODUCTION

Splanchnic ischemia is postulated to be of major importance in the development of multi-organ failure, and death in critically ill patients [1]. The gastrointestinal tract, particularly the stomach is one of the first regions to suffer from hypoperfusion and the last to be restored to normality by resuscitation [2]. These alterations are reflected by increase in the gastric intramucosal pH (pHi) and carbon dioxide [3]. The gastric tonometer measures carbon dioxide tension (PgCO2) in gastric mucosa and helps determine the pHi and the gastric mucosal – arterial carbon dioxide partial pressure difference i.e. PgCO2-PaCO2 gap [4]. The pHi and PgCO2-PaCO2 gap are sensitive markers in the assessment of splanchnic circulation in septic shock [5]. Low pHi and a rising PgCO2-PaCO2 gap are indicative of inadequate tissue perfusion and oxygenation, and are associated with a poor outcome [2, 6]. The effect of hemodynamic drug infusions on the splanchnic circulation has been determined in this study by the measurement of pHi and the PgCO2-PaCO2 gap. These parameters have been used to analyze the effect of various inotropes and vasopressors on the splanchnic circulation in patients with septic shock so as to determine the vasoactive drug combinations with the least as well as maximum deleterious effects.

The aim of this study was to assess the effect of vasoconstrictors on the gastric intra-mucosal pH and PgCo2-PaCO2 gap patients with septic shock using gastric tonometry. The objectives of the study were (a) to investigate the relative effect of vasopressors on splanchnic circulation in terms of the gastric intra-mucosal pHi and the PgCO2-PaCO2 (b) to establish recommendations for the use of inotropes and vasopressors in septic shock to achieve hemodynamic goals with minimal perturbations in splanchnic circulation.

MATERIAL AND METHODS

After obtaining permission from the hospital ethics committee, a prospective observational study of patients in septic shock receiving treatment with different vasopressors was undertaken. Written informed consent was sought from all patients included in the study.

A sample size of 50 patients in septic shock and admitted to intensive care unit (ICU) were included in the study. It comprised of patients with sepsis syndrome on admission as well as those that developed septic shock during the course of stay in the ICU. Patients in the age group of 16 to 80 years of age were included in the study. The diagnosis of sepsis was based on patients having two or more clinical manifestations of systemic inflammatory response syndrome as per guidelines laid down by the American College of Chest Physicians [7]. Terminally ill patients (disseminated malignancy, devastating cerebrovascular accident, CPR with prolonged anoxia), those with age less than 15 years, pregnant women, or where passing a Ryle's tube (and the gastric tonometer catheter) was contraindicated were excluded from the study.

Following the diagnosis of sepsis, a CVP catheter was inserted and fluid resuscitation carried out to a CVP of 8-12 cm of water. If the patient's blood pressure remained low, a gastric tonometric catheter was introduced into the patient's stomach in the same manner as a Ryle's tube and baseline values of mucosal PCO2 obtained. Arterial blood gas analysis was serially undertaken so as to obtain the arterial pH (pHa) and bicarbonate values. The latter were fed into the tonometer which then yielded the pHi. These data recorded prior to the initiation of the inotropes/vasopressors formed the respective baseline values. The monitor was programmed to continuously measure the end-tidal carbon dioxide, gastric mucosal partial pressure of cardon dioxide (PgCO2) and the gastric intramucosal pH (pHi). PgCO2 values were cycled by

the tonometer every 10 minutes, the minimum time required for equilibration of the gastric intramucosal carbon dioxide with the inflated balloon at the tip of the tonometric catheter placed inside the lumen of the stomach.

Vasopressors(Dopamine/Dobutamine/Norepinephrine/Vasopressin/Epinephrine or combinations of these) were started, the choice of pressor being at the discretion of the treating intensivist depending on the clinical situation. The vasopressors were titrated to achieve a mean arterial pressure of >60 mmHg. Changes in pHi were measured by tonometry and recorded on a six - hourly basis along with the respective doses of the vasopressors being administered. The PgCO2 - PaCO2 gap was calculated at each interval by subtracting the former from the latter also at six - hourly intervals. The first recording was made after fluid resuscitation just prior to starting the vasopressor therapy and has been designated as pHi (baseline) and PgCO2-PaCO2 (baseline) respectively. Six- hourly recordings made thereafter have been referred to as pHi (T1), pHi (T2), pHi (T3), and so forth. Correspondingly, similar nomenclature has been applied to the PgCO2-PaCO2 gap recordingsnat T1, T2 and T3 intervals. Data were gathered for each of the 50 subjects over a maximum period of 24 hours or till such a time that the vasopressors were weaned off by the treating intensivist or a terminal event culminating in death took place, whichever occurred earlier. The dose ranges of the intravenous drug infusion used in this study were as follows: dopamine and dobutamine @ 2.5-15 mcg/kg/min, norepinephrine @ 0.05-1.3 mcg/kg/min, epinephrine @ 0.03 – 1.5 mcg/kg/min and low-dose vasopressin @ 0.04IU/min. Statistical analysis was taken to identify the vasopressor/ combination which has the least as well as the maximum deleterious effect on the gastric intramucosal pH and the PgCO2 - PaCO2 gap within the pre-determined dose ranges.

RESULTS

Data were collected from a sample size of 50 patients and a total of eleven drug groups/combinations were formed depending on the vasopressors used. The number of patients in each group is listed as follows (Table 1):

SNo.	Drug/Combination Group	Number of patients
1	Dopamine	26
2	Norepinephrine	27
3	Dopamine - Norepinephrine	14
4	Norepinephrine - Vasopressin	08
5	Dopamine – Norepinephrine - Vasopressin	09
6	Norepinephrine - Dobutamine	07
7	Dopamine – Norepinephrine - Dobutamine	04
8	Norepinephrine – Dobutamine - Vasopressin	02
9	Dopamine - Dobutamine	04
10	Dopamine – Dobutamine - Vasopressin	02
11	Epinephrine	04

Table 1. Various drug groups and the number of patients in each.

A comparison of the mean pHi values between the various drug groups is depicted in Table 2. The mean pHi values in the dopamine group were found to decrease at each interval till the third interval. Thus, dopamine significantly decreased the pHi values for at least three successive readings taken six hours apart ($p<0.001$). The mean pHi values in the norepinephrine group were significantly higher than the baseline ($p<0.001$) at each specified interval (T1, T2 and T3) thereby indicating that norepinephrine had a protective effect on the splanchnic circulation. It was also observed that the addition of norepinephrine to patients receiving dopamine in the dopamine – norepinephrine group significantly increased the mean pHi value as compared to the baseline value for three successive readings. Addition of norepinephrine to dopamine, thus, had a beneficial effect on the pHi. The addition of low – dose vasopressin to patients receiving norepinephrine in the norepinephrine - vasopressin group significantly brought about a decrease in the mean pHi for all the three intervals studied. Therefore, addition of vasopressin event at low doses has a deleterious effect on pHi. An identical deleterious effect on the pHi upon the addition of vasopressin to patients receiving dopamine and norepinephrine in the dopamine-norepinephrine-vasopressin group was observed for all intervals studied. When dobutamine was added to the regime of patients already receiving norepinephrine in the norepinephrine - dobutamine group, there was a significant increase in the mean pHi across all three study intervals (T1-3). Hence, the addition of dobutamine to norepinephrine increased pHi and had a protective effect on the splanchnic circulation. The same effect was also observed in patients receiving a combination of dopamine and norepinephrine in whom dobutamine was added. In the group of patients receiving epinephrine, the mean pHi value was significantly decreased at the third interval. Hence, the use of epinephrine (>18 hours) had an adverse effect of further exacerbating gastric intra-mucosal acidosis.

Drug	Baseline		1st Interval (T1)				2nd Interval (T2)				3rd Interval (T3)			
	Mean	SD	Mean	SD	"t"	"p"	Mean	SD	"t"	"p"	Mean	SD	"t"	"p"
Dopamine	7.362	0.180	7.302	0.199	5.028	**<0.001**	7.215	0.089	6.607	**<0.001**	7.201	0.081	5.822	**<0.001**
Norepinephrine	7.256	0.137	7.286	0.135	-4.733	**<0.001**	7.308	0.138	-7.001	**<0.001**	7.281	0.065	-7.093	**<0.001**
Dopamine- Norepinephrine	7.127	0.110	7.247	0.092	-4.872	**<0.001**	7.252	0.098	-5.619	**<0.001**	7.207	0.073	-6.167	**0.002**
Norepinephrine- Vasopressin	7.255	0.091	7.193	0.097	4.175	**0.004**	7.138	0.068	4.263	**0.004**	7.089	0.117	3.783	**0.009**
Dopamine-Norepinephrine- Vasopressin	7.252	0.081	7.140	0.096	4.243	**0.003**	7.123	0.082	6.755	**<0.001**	7.117	0.081	7.790	**<0.001**
Norepinephrine- obutamine	7.279	0.051	7.306	0.058	-2.875	**0.028**	7.311	0.058	-4.831	**0.003**	7.319	0.078	-3.528	**0.012**
Dopamine-Norepinephrine- obutamine	7.270	0.041	7.315	0.035	-15.588	**0.001**	7.323	0.032	-10.967	**0.002**	-	-	-	-
Norepinephrine-Dobutamine- Vasopressin	7.265	0.021	7.195	0.021	@	@	7.185	0.007	4.00	0.156	7.035	0.191	1.917	0.306
Dopamine- Dobutamine	7.265	0.006	7.285	0.006	-3.464	**0.041**	7.290	0.023	-1.732	0.182	7.285	0.029	-1.155	0.332
Dopamine-Dobutamine- Vasopressin	7.260	0.000	7.220	0.014	4.000	0.156	7.100	0.141	1.600	0.356	6.990	0.269	1.421	0.390
Epinephrine	7.165	0.091	7.010	0.128	1.663	0.195	6.990	0.169	2.555	0.084	6.738	0.214	3.367	**0.044**

@Could not be calculated as both the SDs are same.

Table 2. Paired 't' test for comparison of mean pHi values between the various drug groups. $p<0.05$ implies that the difference from baseline is significant statistically. Figures in bold indicate significant *p* values.

Table 3 depicts the comparison of mean PgCO2 - PaCO2 gap values between the groups studied. In the norepinephrine group, the PgCO2 - PaCO2 gap values observed to be significantly lower in comparison to the baseline mean PgCO2 - PaCO2 gap values at time intervals T1, T2 and T3. Hence, the use of norepinephrine had a beneficial effect on the splanchnic circulation. The PgCO2 - PaCO2 gap was significantly widened at T1 and T2 intervals but not so at the T3 interval in the dopamine group. However, the mean pHi values at T1, T2 and T3 intervals were found to be significantly decreased in

patients in the dopamine group in this study. Therefore, the overall protective effect of this drug on the splanchnic circulation could not be unequivocally established. Conversely, as beneficial effects on both the mean pHi and the mean PgCO2-PaCO2 gap were seen in the norepinephrine group, it inferred that norepinephrine had a definite protective effect on the splanchnic circulation in patients with septic shock.

Drug	Baseline		1st Interval (T1)				2nd Interval (T2)				3rd Interval (T3)			
	Mean	SD	Mean	SD	"t"	"p"	Mean	SD	"t"	"p"	Mean	SD	"t"	"p"
Dopamine	21.000	17.008	26.981	15.988	-4.739	**0.000**	32.950	21.251	-3.659	**0.002**	22.929	16.221	-1.417	0.180
Norepinephrine	25.104	18.331	20.215	14.410	4.805	**0.000**	17.080	12.668	5.190	**0.000**	22.000	12.791	3.893	**0.003**
Dopamine-Norepinephrine	23.286	8.801	13.714	10.695	6.811	**0.000**	14.000	9.439	6.312	**0.000**	10.667	8.824	4.176	**0.009**
Norepinephrine-Vasopressin	13.750	5.312	21.250	8.396	-5.167	**0.001**	24.250	11.222	-4.224	**0.004**	25.000	11.784	-3.075	**0.018**
Dopamine-Norepinephrine-Vasopressin	12.444	11.337	21.556	10.783	-3.355	**0.010**	26.750	10.348	-5.234	**0.001**	32.000	18.089	-7.541	**0.001**
Norepinephrine-Dobutamine	26.286	11.383	21.571	11.326	6.059	**0.001**	16.857	11.052	5.730	**0.001**	16.857	9.616	12.548	**0.000**
Dopamine-Norepinephrine-Dobutamine	28.500	3.109	24.500	2.646	9.798	**0.002**	24.000	0.816	3.781	**0.032**	-	-	0.000	**0.000**
Norepinephrine-Dobutamine-Vasopressin	32.000	0.000	35.000	8.485	-0.500	0.705	56.000	16.971	-2.000	0.295	73.500	12.021	-4.882	0.129
Dopamine- Dobutamine	34.000	1.155	33.000	1.155	@	@	30.500	2.887	4.041	0.027	30.500	6.351	1.347	0.271
Dopamine-Dobutamine- Vasopressin	36.000	0.000	40.000	0.000	@	@	61.000	7.071	-5.000	0.126	81.000	11.314	-5.625	0.112
Epinephrine	43.750	16.276	55.500	24.515	-1.218	0.310	72.750	6.076	-5.295	**0.013**	82.750	3.775	-6.018	**0.009**

@Could not be calculated as both the SDs are same.

Table 3. Paired 't' test for comparison of mean PgCO2 - PaCO2 gap values. $p<0.05$ implies that the difference from baseline is significant statistically. Figures in bold indicate significant *p* values.

Further, the mean PgCO2 - PaCO2 gap values were found to have significantly decreased with respect to the baseline values on the addition of norepinephrine to patients receiving dopamine in the dopamine-norepinephrine group. This observation mirrors the identical effect observed on the mean pHi valued as discussed in the preceding paragraphs. Hence, the addition of norepinephrine to dopamine had a beneficial effect on the splanchnic circulation. When dobutamine was added to norepinephrine or to the dopamine norepinephrine group, the mean PgCO2-PaCO2 gap values were also seen to be significantly decreased as compared to the baseline levels. An identical effect was observed by the improvement in the mean pHi values on introduction of dobutamine as previously mentioned. The addition of vasopressin (low dose) to either norepinephrine or in the dopamine-norepinephrine-vasopressin group resulted in a significant increase in the mean PgCO2-PaCO2 gap values and a significant decrease in the mean pHi values at all mentioned time intervals. Hence, it has been concluded that the use of vasopressin resulted in worsening of splanchnic ischemia. Epinephrine was found to bring about a significant increase in the mean PgCO2-PaCO2 gap values at the second and third intervals (T2 and T3). This effect paralleled the adverse impact of epinephrine on the pHi leading to the conclusion that it exerted a harmful effect on the splanchnic circulation. The summarized results are depicted in Table 4.

Drug Group	Mean pHi	Mean PgCO2-PaCO2 gap	Overall effect on splanchnic irculation
Dopamine	Decreased	Equivocal	Inconclusive
Norepinephrine	Increased	Decreased	Beneficial
Norepinephrine-Dobutamine	Increased	Decreased	Addition of dobutamine to norepinephrine is beneficial
Norepinephrine-Vasopressin	Decreased	Increased	Addition of vasopressin is deleterious
Dopamine-norepinephrine-vasopressin	Decreased	Increased	Addition of vasopressin is deleterious
Epinephrine	Decreased	Increased	Deleterious

Table 4. Summary for inter-group comparison of mean pHi and PgCO2-PaCO2 gap values.

DISCUSSION

The protective role of norepinephrine on the splanchnic circulation, especially so vis-à-vis dopamine, as has been ascertained by this study, has also been determined by other similar studies. Marik and Mohedin [8], concluded that in patients with hyperdynamic septic shock, dopamine was reported to induce a decrease in pHi when compared with norepinephrine. However, De Backer and coworkers [9] did not find any significant difference in the PgCO2 - PaCO2 gaps in a study of patients being treated for septic shock with dopamine or norepinephrine. In another study, Ruokonen and coworkers [10] reported unpredictable effects on splanchnic blood flow in patients with septic shock with norepinephrine.

As stated earlier, the present study could not clearly establish the overall effect of dopamine on the splanchnic circulation in terms of changes in pHi and the PgCO2 – PaCO2 gap . However, dopamine was found to decrease pHi, though its effect on remained PgCO2 – PaCO2 gap equivocal at different time intervals. Several other studies have reported conflicting effects of dopamine on the splanchnic circulation in septic shock. The effect of dopamine on on pHi and PgCO2-PaCO2 gap is in accordance with the findings of some previous studies. These reported that either pHi or PCO_2 gap were unchanged in patients with sepsis treated with low-dose dopamine [11-14]. Jakob and coworkers [15] reported that dopamine administration titrated to achieve a 25% increase in cardiac output induced a significant increase in splanchnic blood flow as measured by more direct means. Other studies have suggested a detrimental effect of dopamine on the splanchnic blood flow. Nevière and coworkers [11] showed that low-dose dopamine (defined as a dose lower than 5 µg/kg/min administered to normotensive patients) decreased gut mucosal blood flow in septic patients. Marik and Mohedin [8] have reported that dopamine, when administered at doses up to 25 µg/kg per min, even decreased pHi. However, given the very small number of patients included in these studies, no definite conclusions could be drawn regarding the effects of dopamine on splanchnic blood flow in septic patients, as reflected in this study. Thus, the effect of dopamine on the splanchnic circulation remains controversial and would need further studies to firmly establish the same. The beneficial effect of dobutamine on the splanchnic perfusion, as inferred by this study, has also been reflected by other studies undertaken by Silva and coworkers [16], Gutierrez and coworkers [17] and Creteur and colleagues [18]. The desirable effect of adding dobutamine to norepinephrine on gastric perfusion as elucidated by the present study has been brought out in a study by Duranteau

and coworkers [19] who used a laser Doppler technique to assess the gastric mucosal blood flow. However, the preferential effect of dobutamine on splanchnic blood flow was not confirmed by Reinelt and coworkers [20].

As per the findings of this study, vasopressin was found to exacerbate gastric intramucosal acidosis and increased the PgCO2-PaCO2 gap even in the low doses that it was used. This detrimental effect of vasopressin has also been shown by Haren and coworkers [21] who in a case series of 11 catecholamine-dependent septic shock patients, showed that vasopressin (0.04 U/min) was responsible for a significant increase in the PgCO2 – PaCO2 gap. In contrast to the results obtained by the present study, Dünser and coworkers [22], who randomly assigned 48 patients with catecholamine-resistant vasodilatory shock to receive a combined infusion of vasopressin and norepinephrine or norepinephrine alone reported that the resultant PgCO2 – PaCO2 gap was significantly lower in patients treated with this combination. The deleterious effect of epinephrine resulting in gastric mucosal acidosis and widening of the PgCO2 - PaCO2 gap that was deduced by the present study, has also been inferred vide a meta-analysis of several studies conducted by Silva et al[16].

Limitations: The number of patients studied was relatively small may be a source of error especially so in certain patient groups in this study. Though groups studied were homogenous at baseline values, the same were compromised subsequently for readings taken at successive time intervals as the group sizes progressively became unequal. Certain drugs such as vasopressin and epinephrine were started only during later stages of treatment by which time there was already a compromise of the systemic as well as splanchnic circulation.

CONCLUSION

In this study, norepinephrine and dobutamine in combination with norepinephrine were found to exert a protective effect on the splanchnic circulation by an improvement in splanchnic perfusion as evidenced by an improving pHi and a decreasing PgCO2 - PaCO2 gap. The overall effect of dopamine on the splanchnic circulation could not be clearly established by this study. However, it has been found to decrease the pHi, though its effect on the PgCO2 – PaCO2 gap remains equivocal. Even in the low doses that vasopressin was used in this study, it exacerbated gastric intramucosal acidosis and increased the PgCO2 - PaCO2 gap. This indicates that vasopressin when used in combination with other agents resulted in worsening of splanchnic ischaemia. Epinephrine was found to exert a deleterious effect on the splanchnic circulation in this study. The use of epinephrine (>18 hours) resulted in worsening of gastric intramucosal acidosis and widening of the PgCO2-PaCO2 gap.

Based on this study, it is concluded that norepinephrine plays a definitive protective role in the prevention of splanchnic ischemia during the management of septic shock. It is the vasopressor of choice in the treatment of septic shock and should be used as the vasopressor of choice during the initial phase of therapy. It may be used in combination with dobutamine so as to further accentuate its protective effect on the splanchnic circulation. In situations in which treatment has been initiated using dopamine, norepinephrine could be added to improve the existing intramucosal acidosis and ischemia. Vasopressin and epinephrine have been found to exert a deleterious effect on the splanchnic circulation in this study. These should be reserved for the treatment of refractory septic shock not responding to initial therapy with other agents or their combinations. The effect of dopamine on splanchnic perfusion needs to be further evaluated by larger, multi-centric trials so as to arrive at a definitive conclusion.

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