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Assessment and Methods of Nutritional Support during Atropinization in Organophosphate and Carbamate Poisoning Cases

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Purpose: Atropine is an antidote used to relieve muscarinic symptoms in patients with organophosphate and carbamate poisoning. Nutritional support via the enteral nutrition (EN) route might be associated with improved clinical outcomes in critically ill patients. This study examined the administration of nutritional support in patients undergoing atropinization, including methods of supply, outcomes, and complications.

Methods: A retrospective observational study was conducted in a tertiary care teaching hospital from 2010 to 2018. Forty-five patients, who were administered with atropine and on mechanical ventilation (MV) due to organophosphate or carbamate poisoning, were enrolled.

Results: Nutritional support was initiated on the third day of hospitalization. Thirty-three patients (73.3%) were initially supported using parenteral nutrition (PN). During atropinization, 32 patients (71.1%) received nutritional support via EN (9) or PN (23). There was no obvious reason for not starting EN during atropinization (61.1%). Pneumonia was observed in both patient groups on EN and PN (p=0.049). Patients without nutritional support had a shorter MV duration (p=0.034) than patients with nutritional support. The methods of nutritional support during atropinization did not show differences in the number of hospital days (p=0.711), MV duration (p=0.933), duration of ICU stay (p=0.850), or recovery at discharge (p=0.197).

Conclusion: Most patients undergoing atropinization were administered PN without obvious reasons to preclude EN. Nutritional support was not correlated with the treatment outcomes or pneumonia. From these results, it might be possible to choose EN in patients undergoing atropinization, but further studies will be necessary.

Key Words: Organophosphate, Poisoning, Atropine, Nutritional support, Enteral nutrition

INTRODUCTION

Organophosphate and carbamate inhibit cholinesterase by blocking the cholinergic receptors, which leads to muscarinic and nicotinic symptoms[1,2]. To alleviate muscarinic symptoms, atropine is known to be an effective antidote[1-3]. Atropinization, which means relieving muscarinic symptoms with atropine, continues until muscarinic symptoms disappear[1-3]. To relieve symptoms related to bronchorrhea and bronchospasm, high dose of atropine should be infused for several days under certain controlled conditions[1-4]. As atropine is an antagonist of muscarinic receptors, it has dose-dependent effects on multiple systems[3-5], including gastrointestinal (GI) transit time[3,6]. Atropine is

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known to reduce the contraction of smooth muscle in the ileum and gastric emptying[6,7]. Complications such as ileus due to atropinization have been reported[8,9]. The effect of atropine on gut motility is the predominant reason for precluding enteral nutrition (EN) support[10].

According to the guidelines for nutritional support in critically ill patients, providing proper nutritional support and early EN is crucial[11-13]. Critically ill patients for over 48 h are at high risk of malnutrition[12]. Malnutrition is often clinically associated with mortality and infectious complications, as addressed by the guidelines on administering adequate nutritional support in critically ill patients[11-13]. Many patients with organophosphate or carbamate poisoning require critical care supports, such as mechanical ventilation (MV); hence, it is important to monitor the status of neurological deterioration and adjust the dosage of atropine accordingly[1,14,15].

This study aimed to observe the administration of nutritional support in patients with organophosphate or carbamate poisoning, including methods of nutritional support during atropinization. We also aimed to determine the relationship between nutritional support and treatment outcomes and infectious complications.

METHODS

1. Study design and participants

A retrospective observational study was conducted in a single intensive care unit (ICU) of a tertiary care teaching hospital. This study was approved by the institutional review board of our hospital (AJIRB-MED-MDB-19-210). From January 2010 to July 2018, patients who were admitted to ICU owing to organophosphate or carbamate poisoning were included. Patients under 18 years of age were excluded. Patients in whom atropinization were stopped within 1 day because they were free of muscarinic symptoms or without organophosphate or carbamate poisoning were excluded. Patients who were admitted owing to cardiac arrest, who were not intubated, who were discharged within 48 hours after admission, and who died within 48 hours after admission were also excluded. Toxicologic management and intensive care support were performed according to the protocol of this hospital.

2. Data collection

Medical records of the patients were reviewed. Data on demographics, symptoms related to poisoning, laboratory investigation, and treatment related to poisoning were collected. Data on intensive care supports including vasopressors and MV, as well as sequential organ failure assessment (SOFA), were also collected. To assess the severity in patients with acute symptoms of organophosphate or carbamate poisoning, SOFA was collected[16]. Nutritional screening results, nutritional support methods, dates of initiation of treatment, amount of support at day 3 after admission, and complications related to nutritional support were reviewed. Outcomes including hospital day (HD), MV duration, and ICU stay duration were collected. Recovery at discharge was reviewed and patients were divided into three groups (good recovery, partial recovery, died or serious sequelae) as presented in a previous study[14].

3. Quantitative variables

Nutritional risk screening (NRS) was performed within 24 hours from admission by a nutritionist using the screening tool of this hospital. The NRS method used at this hospital identifies patients based on three groupings (high-risk, moderate-risk, and low-risk). Demanded calories and proteins were provided by the nutritional support team (NST) in the ICU. Nutrition support method was chosen by the physician, referring to the opinion of NST.

4. Statistical methods

Data for continuous variables with non-normal distribution were reported as median with interquartile range (IQR). The Mann-Whitney test or Spearman's correlation analysis was used to compare the continuous variables. Categorical variables were expressed as frequencies and percentages, and comparisons were performed using the Fisher's exact test. Data were analyzed using SPSS ver. 20.

RESULTS

1. Participants

There were 98 organophosphate or carbamate intoxicated patients who were above 18 years of age. Thirty-four patients without muscarinic symptoms or poisoning evi-

dence were excluded. Five patients with cardiac arrest and six patients without intubation were excluded. Five patients who died within 48 hours and three patients who were discharged within 48 hours were excluded. Finally, 45 patients were included in the study.

2. Patients treated with atropine

A total of 36 patients (80%) had poisoning due to organophosphate and seven patients (15.6%) due to carbamate (Table 1). Median values for serum cholinesterase level was 457.0 U/L, dosage of atropine was 658.9 mg, and duration of infusion was 5.0 days (3.0-7.0). Thirty patients (66.7%) were fully recovered and 10 patients (22.2%) died or had serious sequelae. The dosage of atropine administered was correlated with serum cholinesterase level (r=-0.548, p=0.000) and not correlated with SOFA (r=-0.006, p=0.967). The dosage of atropine was also correlated with HD (r=0.538, p=0.000),

MV duration (r=0.566, p=0.000), and length of ICU stay (r=0.505, p=0.000), but not with recovery at discharge (p=0.273). Serum cholinesterase level was not correlated with SOFA (r=-0.110, p=0.473), HD (r=-0.206, p=0.174), MV duration (r=-0.249, p=0.099), length of ICU stay (r=-0.220, p=0.147), and recovery at discharge (p=0.693).

3. Characteristics of the nutritional support

Fifteen patients (33.3%) showed moderate to high risk using NRS at admission (Table 1). Nutritional support was started at day 3. Total parenteral nutrition (TPN) was the most common method of initial nutrition supply (73.3%). The method of initial nutritional support was neither correlated with SOFA nor serum cholinesterase level. The median duration of PN initiation (3.0 days) was shorter than that of EN (3.5 days) and was not significantly different. Although PN supplied a higher ratio of calories and proteins at 72

Table 1. Clinical characteristics of patients according to the starting method of nutritional support

	Total (n=45)	EN (n=12)	PN (n=33)	p-value
Age (years)	69.0 (54.50-77.50)	68.0 (50.50-73.75)	70.0 (54.50-80.00)	0.464
Poisoned material (%)				
Organophosphate	36 (80)	8 (66.7)	28 (84.8)	0.249
Carbamate	7 (15.6)	3 (25.0)	4 (3.0)	
Unknown	2 (4.4)	1 (8.3)	1 (3.0)	
Intentional exposure (%)	38 (84.4)	12 (100)	26 (78.8)	0.094
Dosage of atropine (mg)	658.9 (329.26-1152.30)	513.7 (193.13-907.88)	773.3 (389.05-1206.95)	0.305
Initial cholinesterase (U/L)	457.0 (230.00-1941.00)	555.5 (203.00-1578.50)	457.0 (243.00-2042.50)	0.488
GCS	6.0 (4.00-8.00)	5.5 (4.00-10.00)	6.0 (3.0-7.0)	0.161
Starting day of NS	3.0 (2.00-4.50)	3.5 (2.25-5.50)	3.0 (2.00-4.50)	0.547
SOFA	8.0 (6.00-10.00)	8.0 (6.00-9.75)	8.0 (6.00-10.50)	0.689
NRS (%)				
Low risk	30 (66.7)	9 (75.0)	21 (63.6)	0.880
Moderate risk	7 (15.6)	1 (8.3)	6 (18.2)	
High risk	8 (17.8)	2 (16.7)	6 (18.2)	
Supplied calories (%)*	69.8 (23.48-103.03)	33.6 (7.24-85.38)	79.5 (28.38-104.99)	0.050
Supplied protein (%)*	55.6 (0.00-96.00)	13.1 (0.00-60.40)	72.7 (0.00-102.56)	0.051
Day of full supply	5.0 (3.0-7.0)	5 (4.0-8.5)	4 (3.0-7.0)	
Intolerance (%)				
Vomiting	1 (2.2)	0 (0.0)	1 (3.0)	0.709
Diarrhea	5 (11.1)	2 (16.7)	3 (9.1)	
Pneumonia (%)	2 (4.4)	1 (8.3)	1 (3.0)	0.467
Hospital day	21.0 (14.50-28.50)	17.5 (11.50-27.50)	21.0 (15.00-34.50)	0.154
ICU stay	18.0 (12.50-24.0)	17.5 (10.50-20.75)	18.0 (13.50-24.50)	0.504
Duration of MV	14.0 (9.50-20.00)	10.0 (4.75-15.00)	16.0 (10.50-21.50)	0.024
Recovery at discharge (%)				
Good recovery	30 (66.7)	8 (66.7)	22 (66.7)	0.766
Partial recovery	5 (11.1)	2 (16.7)	3 (9.1)	
Died or serious sequelae	10 (22.2)	2 (16.7)	8 (24.2)	

Values are expressed as median (Q1-Q3) or N (%), * ratio of supplied calories or proteins to demanded calories or proteins, EN: enteral nutrition, PN: parenteral nutrition, NS: nutritional support, GCS: Glasgow Coma Scale, SOFA: sequential organ failure assessment, NRS: nutritional risk screening, ICU: intensive care unit, MV: mechanical ventilation

Table 2. Characteristics of patients according to nutritional support methods during atropinization

	No NS (n=13)	EN (n=9)	PN (n=23)	p-value*
Dose of atropine (mg)[+]	223.9 (162.30-517.25)	914.5 (544.90-2384.10)	816.6 (497.90-1156.60)	0.187
Starting day of NS[+]	5.0 (3.50-6.50)	3.0 (2.00-4.00)	3.0 (2.00-4.00)	0.983
Starting method of NS (%)				0.003
EN	6 (46.2)	5 (55.6)	1 (4.3)	
PN	7 (53.8)	4 (44.4)	22 (95.7)	
Initial cholinesterase (U/L)[+]	1208.0 (340.50-4818.50)	230.0 (200.00-846.50)	373.0 (230.00-2003.00)	0.136
SOFA	8.0 (5.00-9.50)	8.0 (5.50-11.50)	8.0 (7.00-10.00)	0.952
NRS (%)				0.284
Low risk	9 (69.2)	4 (44.4)	17 (73.9)	
Moderate risk	1 (7.7)	3 (33.3)	3 (13.0)	
High risk	3 (23.1)	2 (22.2)	3 (13.0)	
Supplied calories (%)[+ +]	23.5 (11.65-57.69)	69.3 (35.85-89.08)	89.4 (66.67-115.03)	0.190
Supplied protein (%)[+ +]	0.0 (0.00-16.67)	52.3 (13.06-67.38)	94.5 (55.56-111.11)	0.022
Day of full supply[+]	7.0 (4.5-9.0)	7.0 (4.0-8.0)	3.0 (2.0-5.0)	0.030
Intolerance (%)				0.038
Vomiting	0 (0.0)	1 (11.1)	0 (0.0)	
Diarrhea	0 (0.0)	3 (33.3)	2 (8.7)	
Pneumonia (%)	0 (0.0)	1 (11.1)	1 (4.3)	0.490
Hospital day	19.0 (15.00-25.50)	18.0 (14.00-28.50)	23.0 (14.00-39.00)	0.711
ICU stay	18.0 (11.50-19.50)	18.0 (11.50-24.00)	18.0 (13.00-26.00)	0.850
Duration of MV[+]	11.0 (7.00-15.50)	16.0 (10.00-23.50)	16.0 (10.00-23.00)	0.933
Recovery at discharge (%)				0.197
Good recovery	12 (92.3)	3 (33.3)	15 (65.2)	
Partial recovery	0 (0.0)	2 (22.2)	3 (13.0)	
Died or serious sequelae	1 (7.7)	4 (44.4)	5 (21.7)	

Values are expressed as median (Q1-Q3) or N(%), * p-value are calculated between EN group and PN group, [+] Variables showed p-value<0.05 comparing no NS group and NS group; [+] Ratio of supplied calories or proteins to demanded calories or proteins at day 3, NS: nutritional support, EN: enteral nutrition, PN: parenteral nutrition, GCS: Glasgow Coma Scale, SOFA: sequential organ failure assessment, NRS: nutritional risk screening, ICU: intensive care unit, MV: mechanical ventilation

Table 3. Reasons for not choosing enteral nutritional support during atropinization

Reasons	Number of patients (%)
For no obvious reason	22 (61.1%)
Early tapering of atropine	4 (11.1%)
Ileus	3 (8.3%)
Pancreatitis	2 (5.6%)
Failure of extubating	2 (5.6%)
Death	2 (5.6%)
Shock	1 (2.8%)

hours after admission compared to EN, the difference was not significant. The MV duration of patients starting nutritional support via EN was shorter than that of patients starting nutritional support via PN (p=0.024). Other variables were not significantly different between the two groups.

4. Nutritional support for patients undergoing atropinization

Thirty-two patients (71.1%) were prescribed with nutri-

tional support during atropinization (Table 2). Patients without nutritional support had a shorter MV duration (p=0.002) and a lower dosage of atropine (p=0.000), compared to patients receiving nutritional support (Table 2). The starting day of nutritional support was not correlated with dosage (r=0.010, p=0.947) or MV duration (r=0.057, p=0.711) during atropinization. The initial cholinesterase level in patients without nutritional support was higher than that in patients with nutritional support (p=0.035). Patients without nutritional support had a shorter MV duration (p=0.034). HD (p=0.270), duration of ICU stay (p=0.460), and recovery at discharge (p=0.078) were not significantly different.

During atropinization, EN was provided to nine patients (20%) and PN to 23 patients (51.1%) (Table 2). Of whom, four patients (8.9%) started nutritional support via PN and converted to EN during atropinization. The duration of atropinization was longer in patients with EN during atropinization than in patients with PN (p=0.046) or no nutritional support (p=0.002). There was no obvious reason for not starting EN during atropinization in 61.1% of patients (Table 3). Early tapering of atropine within 48 hours was the next

most common reason (11.1%). There were no differences in the dosage of atropine, cholinesterase level, or SOFA between patients receiving EN and PN. Diarrhea and vomiting were more prevalent during atropinization in patients with EN than those with PN (p=0.01). EN was stopped in two patients owing to severe diarrhea and vomiting. One patient presented with vomiting had have an episode of refractory shock with high-dose vasopressor a day before vomiting. Development of pneumonia after starting nutritional support was shown in one patient each for EN and PN. The methods of nutritional support during atropinization did not show any differences in HD, MV duration, duration of ICU stay, or recovery at discharge.

DISCUSSION

This study characterized the administration of nutritional support in patients undergoing atropinization, especially according to methods of nutrition, related complications, and the effects of nutritional support. Thirty-three patients (73.3%) of whom surveyed had TPN as initial nutritional support. During atropinization, 20% of patients received nutritional support via EN. In total, 61.1% of patients did not receive EN without specific contraindications. There was no statistical difference in the outcomes according to whether initial nutritional support was given, or methods during atropinization.

Atropine has cholinergic effects and is used as an antidote for organophosphate and carbamate poisoning[3-5]. In severe organophosphate and carbamate poisoning cases, fatality has been reported to be about 9.7 to 20%[1,14,15,17]. Patients usually die from hemodynamic instability with respiratory failure due to bronchorrhea and mental status change[1,4,14]. Therefore, active resuscitation aiming at relieving muscarinic symptoms is one of the key interventions to the treatment of organophosphate and carbamate poisoning[1,4,5]. Atropinization aims to resolve muscarinic symptoms by using atropine for the treatment of organophosphate poisoning[1,2,4,5]. Signs of atropinization are clear lungs without bronchorrhea, adequate blood pressure (systolic blood pressure of 80-90 mmHg), and adequate heart rate (above 80 bpm)[1,4,5]. Commonly recommended atropinization treatment regime is to give 1-3 mg of atropine followed by continuous infusion of 0.4-4 mg/h for several hours[3,4]. Another treatment method is to give atropine 2-5 mg every 10-15 minutes until the state of atropinization is achieved[3-5]. A doubling dose of bolus administration is also recommended[18]. By using these methods, a high dosage of atropine could be used to achieve atropinization in patients[1,2,4,5]. The mean dosage of atropine was reported as 23.4 mg, but a higher dosage up to 380 mg has also been reported[4,14,18,19]. Atropine also causes side effects during atropinization[3,20]. Mild complications such as higher heart rate or dry mouth were considered signs of atropinization and resolved toxicity of organophosphate[1-3]. However, patients are also at risks of serious complications such as delirium or coma[3]. At high dosage, atropine is known to have an effect on gastric emptying time and bowel contractility[3,7-9]. A previous study reported that atropine delayed gastric emptying resulting in delayed mouth-to-ileum transit[6]. However, cases of ileus are rarely reported in commonly used dosages[8,9,21]. In addition, ileus might not be a critical complication of atropine. Beards and colleagues considered the development of ileus during atropinization as a sign of recovery in red blood cell cholinesterase and recovery from poisoning[8]. In our study, three patients (6.7%) presented with symptoms of ileus. Although the median dosage of atropine (658.9 mg) was higher than those reported in previous studies, ileus was rare and had no critical complications.

In ICU patients, nutritional support is an important factor affecting treatment outcomes and infectious complications[11,13]. Prevailing guidelines recommend nutritional support in ICU patients using EN if oral feeding is not possible[11,12]. EN is known to prevent atrophy of the intestinal mucosa and help maintaining the structure and function of the gastrointestinal mucosa[11]. In particular, early EN within 48 hours had an advantage over delayed EN on mortality and infectious complications[11,12]. The indications for delayed EN include refractory shock with high-dose vasopressor, uncontrolled hypoxia or acidosis, bowel ischemia, high output fistula, abdominal compartment syndrome, loss of bowel continuity, uncontrolled upper gastrointestinal bleeding, and high gastric residual volume[11-13]. However, use of medications affecting bowel motility or gastric emptying time is not an indication for the delay EN[11-13].

In our study, only 20% of patients were supplied with EN support during atropinization. However, we found that 61.1% of patients did not have the indications to delay EN. There might be several barriers to not starting EN during atropinization. According to prevailing guidelines, in hemodynamically unstable patients undergone high-dose vasopressors, EN should be delayed without confirming the airway conditions[11-13]. This is because bronchorrhea due to anticholinergic toxicity could prohibit the initiation of EN[1,2]. Diarrhea due to organophosphate toxicity can also be one of the rea-

sons not to start EN[22]. Pancreatitis is frequently presented in organophosphate or carbamate poisoning cases, which can be an indication to delay EN[1,2]. In summary, these are the recommended indications to delay EN[11-13]. In addition, fearing of ileus caused by atropine might be one of the reasons of previously reported cases[6,8,9,21]. Moses et al.[10] reported that atropinization precludes early EN because of atropine's effect on gut motility, indicating possible mucosal injuries due to organophosphate and carbamate can be another reason not to start EN during atropinization[1,2].

Otherwise, previous studies have reported that EN during atropinization are of low risk[10,23]. In a randomized study, the difference in treatment outcomes and infectious complications between groups postponed nutritional support until 7 days and the group with hypocaloric EN was compared[10]. Although there were no advantages in clinical outcomes, and infectious complications in the group with hypocaloric EN, researchers concluded that EN with atropinization was safe with caution as there was no development of serious complications[10]. Yan et al.[23] also studied mucosal injury in organophosphate poisoning by assigning patients into 24-hour EN and 48-hour EN groups. They found that bowel mucosal injury was obvious up to 144 hours[23]. However, the intestinal permeability of the intoxicated group was preserved compared to that of the normal control group[23]. They reported that early EN is not harmful and might be helpful in the management of treatment for organophosphate poisoning[23].

We also compared the differences according to the prescription and methods of nutritional support. There was no difference in other treatment outcomes and development of pneumonia between patients with nutritional support and those without nutritional support (Table 2). Patients without nutritional support had lower dosages of atropine and higher cholinesterase levels than their counterparts[10]. Although we cannot specify the reasons not starting nutritional support in this group, patients without nutritional support had mild muscarinic symptoms. In these patients, there was no chance of starting nutritional support owing to the short duration of atropinization (median 2.0). We also compared the differences between patients with EN and patients with PN during atropinization. The duration and dosage of atropinization and cholinesterase levels were not correlated with the methods of nutritional support. Although patients with EN had more frequent vomiting and diarrhea, there was no difference in the treatment outcomes and development of pneumonia. Vomiting and diarrhea are frequently present in crit-

ically ill patients supported with EN and these are not the contraindications to delay EN[13,22]. We did not find any barriers or complications to start EN during atropinization.

This study has several limitations. Firstly, this study was conducted retrospectively in a single center with a small sample size, and the results may lack the scientific validity required for generalization of research findings, and a small sample size in clinical trials may not yield a valid conclusion. Secondly, we cannot describe the reasons not starting nutritional support and the factors affecting the choice of nutritional support method. Further study would be helpful to identify factors related to choosing the methods of nutritional support. Thirdly, the nutritional risk was low in this study population. Therefore, nutritional support might not have a significant effect on treatment outcomes and infectious complications in this study. Fourthly, the severity score performed at admission was higher in this study compared to a previous study[16]. We selected patients on MV in the ICU to identify the tendency of choosing a specific nutritional support method. This might have been a selection bias in this study. Finally, we excluded patients who died within 48 hours because we wanted to find the difference according to nutritional supplemental methods, hence, patients who could not receive EN within 48 hours were excluded.

CONCLUSION

In conclusion, most patients undergoing atropinization owing to organophosphate or carbamate poisoning were nutritionally supported via PN. There was no obvious reason not to start EN during atropinization in most cases. The method of nutritional support during atropinization was not correlated with treatment outcomes or development of pneumonia. Although a large prospective study would be helpful, it might be available to start nutritional support via EN in patients undergoing atropinization owing to organophosphate and carbamate poisoning.

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