Ind. J. Pharm. Edu. Res., 2024; 58(3):794-801.
https://www.ijper.org

Original Article

Comparison of Normal saline, Activated Charcoal and Intravenous Lipid Emulsion in a Rat Model of Colchicine Overdose: Experimental Study

Mustafa Ferudun Çelikmen[1], Sezgin Sarikaya[1], Doğaç Niyazi Özüçelik[2,*], Fadime Canbolat[3], Engin Sümer[4], Elif Çiğdem Keleş[5], Deniz Sema Maktav Çelikmen[6]

[1]Department of Emergency, Medicine Faculty, Yeditepe University, Istanbul, TURKEY.
[2]Department of Social Work, Health Science Faculty, Istanbul University-Cerrahpasa, Istanbul, TURKEY.
[3]Department of Pharmacy Services, Vocational School of Health Services, Çanakkale Onsekiz Mart University, Çanakkale, TURKEY.
[4]Department of YUDETAM, Faculty of Medicine Experimental Research Center, Yeditepe University, İstanbul, TURKEY.
[5]Department of Biostatistics and Medical Informatic, Faculty of Medicine, Yeditepe University, Istanbul, TURKEY.
[6]Departmeny of Internal Medicine, Medical Park Goztepe Hospital, Internal Medicine, Bahcesehir University, Istanbul, TURKEY.

ABSTRACT

Aim: The aim of this study is to investigate the effects of Normal Saline (NS), Activated Charcoal (AC) and Intravenous Lipid Emulsion (ILE) in colchicine poisonings that resulted in death. **Study Design:** The research is an experimental study carried out in a medical school animal laboratory. **Materials and Methods:** 24 female Sprague-Dawley rats were divided into 4 equal groups. After giving Colchicine (1 mg/kg, PO) to all animals, different treatments (NS, AC, ILE) were given to 3 groups. Group 4 was not treated. Colchicine blood samples (0.8 mL) were taken from the vena jugularis externa at 4, 8 and 24 hr and evaluated by liquid chromatography. **Results:** While the blood colchicine level decreased in all groups at 24 hr, the highest decrease was observed in the AC group. Compared to the 4th hr, blood colchicine levels at 8 hr decreased by 15.49% in the NS group, 64.55% in the AC group and 34.56% in the ILE group. Blood colchicine levels at 24 hr decreased by 66.1% in the NS group, 73.12% in the AC group, 37.73% in the ILE group and 59.17% in the untreated group compared to the 8th hr. **Conclusion:** AC administration is very effective in lowering blood colchicine levels. ILE can be used with NS and AC as an early treatment option for colchicine overdoses. However, further studies are needed for more effective methods in the treatment of colchicine overdose.

Keywords: Colchicine overdose, İntoxication, Normal saline, Activated charcoal, İntravenous lipid emulsion.

Correspondence:
Prof. Dogac Niyazi Ozucelik, MD
Health Science Faculty, Istanbul University-Cerrahpasa, Istanbul, TURKEY.
Email: dogacniyaz@gmail.com, dogacniyazi.ozucelik@iuc.edu.tr
ORCID ID: 0000-0002-7752-0667

Received: 16-08-2023;
Revised: 13-02-2024;
Accepted: 14-05-2024.

INTRODUCTION

Colchicine is a neutral, gastrointestinal-absorbed lipophilic and anti-inflammatory alkaloid obtained from the plant colchicum autumnale. It is known to be beneficial primarily in gout attacks and Familial Mediterranean Fever (FMF) treatment, as well as in primary biliary cirrhosis, alcoholic cirrhosis, psoriasis, necrotizing vasculitis, amyloidosis, sarcoidosis and scleroderma. The oral bioavailability of colchicine ranges from 18% to 79%. 1 mg PO of colchicine reaches its peak plasma concentration after 0.5 to 1.5 hr. The half-life in healthy people ranges from 23 to 41 hr.[1,2] Colchicine is primarily metabolized by the liver, undergoes significant enterohepatic circulation and is excreted by the kidneys.

Although colchicine intoxication with a narrow therapeutic index is rare, its potentially life-threatening risk is high. According to the 2009 report of the American Association of Poison Control Center, the annual incidence of colchicine poisoning under the age of 19 was 0.0046%.[3] In a study published in Turkey, which included 23 cases between the ages of 0-16, 13% of patients with colchicine poisoning died.[4]

Colchicine-related death usually occurs 36-72 hr after ingestion as a result of central nervous system toxicity, hypovolemic shock, cardiovascular collapse, or rapidly progressive multi-organ failure.[3-5] The mechanism of death in colchicine toxicity has been associated with disruption of protein assembly. This results in decreased endocytosis and exocytosis, decreased cell motility, arrest of cardiac myocyte conduction, cardiac arrest and multi-organ failure.[6]

DOI: 10.5530/ijper.58.3.87

At doses below 0.5 mg/kg of colchicine, minor toxicity develops and 100% recovery is observed. At doses between 0.5-0.8 mg/kg of colchicine, major toxicity develops and 10% mortality occurs. However, at doses above 0.8 mg/kg, patients have been reported to die as a result of cardiogenic shock within 72 hr. However, it is known that the amount of medication taken is not directly proportional to the severity of clinical findings and prognosis.[7,8]

In animal and human studies, chromatography is recommended for the detection of colchicine in body fluids (such as serum, urine, milk) and tissues due to its rapid distribution and lability in the body. Chromatography is a widely used analytical technique to separate a mixture of chemicals into its components so that individual components can be analyzed in detail.[9-16]

Unfortunately, an effective treatment method has not been demonstrated for colchicine intoxication, which has a high mortality rate. Because colchicine is rapidly absorbed, rapidly distributed and bound to tissues after oral intake, treatment consists of gastric decontamination, Activated Charcoal (AC), fluid and electrolyte replacement and supportive care within the 1st hr.

It has been emphasized that treatments such as oral AC or hemodialysis are insufficient in colchicine intoxications and that although methods such as ColchiFab are effective, there is a commercial difficulty in their application.[6,17-20]

In recent years, İntravenous Lipid Emulsion (ILE) application has been used especially in poisoning with lipophilic drugs. However, in human poisonings, adequate information and standardization have not been provided yet regarding the dose, method of administration and side effects.[21] It is known that ILE is beneficial against the toxicity caused by almost all Local Anesthetics (LA) including bupivacaine.[22-24]

The efficacy of ILE is defined as the capture of lipophilic drugs in a plasma lipid compartment ("lipid sink"). The emulsion acts as a lipid pool that surrounds and inactivates the lipophilic drug molecule. This lipid compartment removes the drug from toxicity-sensitive organs and accelerates its redistribution to organs where it is stored, detoxified and subsequently excreted.[25]

In a few studies, the efficacy of ILE has been shown in verapamil, chlorpromazine, bupropion, lamotrigine, haloperidol, herbicide, tricyclic antidepressant, calcium channel blocker, beta blocker and digoxin intoxications as well as LAs.[26,27]

Whether ILE has an effect on colchicine intoxication has not been investigated to date. The aim of this study is to evaluate the effects of ILE in rats given colchicine by liquid chromatography and compare it with Normal Saline (NS) and AC treatment used in the general intoxication approach.

MATERIALS AND METHODS

Study Design and Settings

This experimental study was conducted after obtaining approval from Yeditepe University Animal Research local ethics committee (number: 632; date of decision: 22.12.2017). It was carried out at Yeditepe University Faculty of Medicine Experimental Research Center. In this experimental study, animals were divided into groups for different treatment applications. Blood samples were taken from all animals before and after treatment. Differences between blood colchicine levels were evaluated by chromatography.

Experimental Animals

In this study, 24 female Sprague-Dawley rats, each weighing approximately 300 g, were used. 24 hr before the start of the study, animals were housed in metal cages in a controlled environment at 22°C with a 12 hr light/dark cycle. 24 rats were divided into 4 groups, each containing 6 rats.

Anesthesia

All rats were administered tail vein of 80 mg/kg Ketamine Hydrochloride and 10 mg/kg Xylazine (Rompun vial; Bayer AG, Leverkusen, Germany) during intervention and during surgery. No additional dose was required.

Animal groups

Colchicine and AC were administered to all animals through an Orogastric tube. NS and ILE were administered via the tail vein of the animals (26 G via catheter). Animal groups and given treatment practices are summarized below:

Group 1 (n=6): Colchicine (1 mg/kg, PO) was given, while 5 mL/kg IV bolus of Normal Saline was given concurrently.

Group 2 (n=6): Activated Charcoal (1 g/kg, PO) was given 30 min after Colchicine (1 mg/kg, PO).

Group 3 (n=6): ILE (20%) Lipid Emulsion IV (5 mL/kg IV bolus and 0.5 mL/kg/min IV, 10 min infusion) was given 30 minutes after Colchicine (1 mg/kg, PO) was given.

Group 4 (n=6): Colchicine alone (1 mg/kg, PO) was given. No treatment was applied.

Biochemical and Colchicine Examination

Blood sample (0.8 mL) was taken from all animals before any drug administration. Blood samples (0.8 mL) were taken again from the vena jugularis externa at 4 and 8 hr for blood colchicine levels. At the end of 24 hr, all animals were sacrificed with high-dose anesthesia and blood samples (0.8 mL) were taken again at 24 hr. The samples were centrifuged for 10 min and 3000 spins at 4°C. It was stored at -20°C in Yeditepe University Faculty of Medicine

Biochemistry laboratory. Plasma concentration of colchicine was measured with a liquid chromatography device.

Standards and Reagents

Colchicine and the deuterated compounds used as internal standards colchicine-d3 were purchased from sigma. Also, all HPLC solvents and organic solvents were purchased from Merck.

Preparation of Calibration Standards and Quality Control Samples

Stock standard solution of Colchicine was prepared by dissolving accurately weighed standards in methanol (C: 0,1 mg/mL). Colchicine stock standard solution was then diluted with Methanol: Water [30:70, V/V] to achieve a dilute standard solution at the concentration of 250 µg/mL for Colchicine. This dilute standard solution was used in preparation of calibration standards and quality control samples. Internal Standard [IS] Colchicine-d3 stock solution was prepared by dissolving accurately weighed 1 mg in 100 mL Methanol [0.01 mg/mL] and internal standart working solution was prepared by diluting this solution to 10 ng/mL in Methanol: Water [30:70, V/V]. All solutions were stored at 4°C when not used. Appropriate volumes of dilue standard solution were spiked to blank serum to prepare eight calibration standards and three quality control samples. The calibration standards included concentrations of 5.0, 10.0, 20.0, 40.0, 60.0, 80.0, 100.0, 120.0 ng/mL for Colchicine. The quality control samples included concentrations of 15.0, 60.0, 100.0 ng/mL for Colchicine.

Chromotography

HPLC (High Performance Liquid Chromatography) was performed on an Agilent 1200 HPLC system. It was performed using an X Terra RP18 analytical column (3 mm x 150 mm; 3.5 um). Mobile phase A was deiyonize water with formic Acid (250:1, V/V) and mobile phase B was Methanol. Gradient system conditions were as follows: 90% mobile phase A for 1 min. From 1.10 min to 10 min, 20% mobile phase A. From 10.10 min to 12 min, 90% mobile phase A. Total analysis run time was 12 min. at a flow rate of 0.5 mL/min.

Quantification

MS/MS was performed on an Agilent 6410 B triple-quadrupole LC-MS/MS using an electrospray ionization (ESI) source. Ion source parameters for the analysis were gas temp=350°C, gas flow=10 L/min, nebulizer=50 psi and capillary voltage=4000 V. Quantitative analysis was carried out by multiple reaction mode with an Electrospray positive ionization (ES+). Quantitation was based on monitoring precursor ion and product ion for colchicine m/z 400.2>310.3 and for internal standart Colchicine-d3 m/z 403.3>359.2. Eight calibrators and three quality controls were prepared in human blank serum. Concentrations were calculated by comparison of peak-area ratio of Colchicine and internal standard Colchicine -d3 against a seven-point calibration curve using a 1/x linear curve fit. Quantitation parameters are detailed in Table 1.

Extraction

100 µL of internal standart working solution (C: 10 ng/mL) and 200 µL cold acetonitrile were added to the 200 µL serum sample, vortexed for 30 sec and centrifuged at 16162 x g for 5 min. Five µL was injected into the analytical system.

Statistical Methods

Statistical analyzes were performed using NCSS statistical software (NCSS LLC, East Kaysville, UT, USA; 2007). Mean, median, minimum, maximum and standard deviation were used as descriptive statistical methods. Wilcoxon test was used for intragroup comparisons, Mann Whitney U test and Kruskal Wallis test were used for intergroup comparisons. A p value of <0.05 was accepted for statistical significance.

RESULTS

In all groups, blood colchicine levels were found to be high in blood samples taken at 4th hr after administration of Colchicine (1 mg/kg, PO). There was no statistically significant difference between the groups at the 4th hr (p>0.05) (Table 2).

In the blood samples taken at the 8th hr, blood colchicine level decreased in all treatment groups (NS, AC, ILE), while blood colchicine level increased in the untreated 4th group. At the 8th hr, blood Colchicine level decreased the most in the 2nd group given AC (2.77867 ng/mL), followed by the 3rd group (1.675 ng/mL) given ILE and the 1st group (0.7785 ng/mL) given NS. Compared to the 4th hr, blood colchicine levels at the 8th hr decreased by 15.49% in the NS group, decreased by 64.55% in the AC group and decreased by 34.56% in the ILE group. The blood colchicine level in the 4 groups that did not receive treatment increased by 43.91% (1,89867 ng/mL) at the 8th hr compared to the 4th hr. The difference between the blood colchicine levels between

Table 1: Colchicine quantitation parameters in study.

Compound name	Retention time (min)	Precursor (m/z)	Quantifier product mass (m/z)	Fragmentor voltage	Quant collision energy	Cell Accelerator voltage	Polarity	Internal Standard
Colchicine	3.05	403.3	359.2	80	20	7	+	Colchicine-d3
Colchicine-d3	3.05	400.2	310.3	85	25			-

Table 2: Levels of colchicine in the 4, 8 and 24 hr in rats.

Times	Groups	Mean±SD (ng/mL)	Median (Min-Max)	*p**
4 hr	Group 1 (Colchicine+NS)	5.02533±1.045530	4.89950 (3.664-6.609)	0.870
	Group 2 (Colchicine+AC)	4.30450±2.959107	4.56100 (0.103-8.674)	
	Group 3 (Colchicine+ILE)	4.84567±2.214818	4.70350 (2.351-8.164)	
	Group 4 (Colchicine)	4.32333±1.587975	4.14750 (2.870-6.557)	
	Total	4.62471±1.964896	4.88000 (0.103-8.674)	
8 hr	Group 1 (Colchicine+NS)	4.24683±1.550714	3.58800 (2.969-6.919)	0.004
	Group 2 (Colchicine+AC)	1.52583±1.017607	1.30750 (0.606-3.468)	
	Group 3 (Colchicine+ILE)	3.17067±0.737924	3.14950 (2.281-4.076)	
	Group 4 (Colchicine)	6.22200±3.937860	4.26400 (3.592-13.430)	
	Total	3.79133±2.696677	3.51000 (0.606-13.430)	
24 hr	Group 1 (Colchicine+NS)	1.43933±0.432404	1.58200 (0.788-1.832)	0.003
	Group 2 (Colchicine+AC)	0.41000±0.333596	0.28200 (0.140-1.025)	
	Group 3 (Colchicine+ILE)	1.97433±0.629807	2.05550 (1.129-2.700)	
	Group 4 (Colchicine)	2.54017±1.651543	1.61450 (1.185-4.705)	
	Total	1.59096±1.177807	1.49950 (0.140-4.705)	

NS: Normal Saline; ILE: Intravenous Lipid Emulsion; AC: Activated Charcoal; Min: Minumum; Max: Maximum; *p**Kruskal-Wallis test.

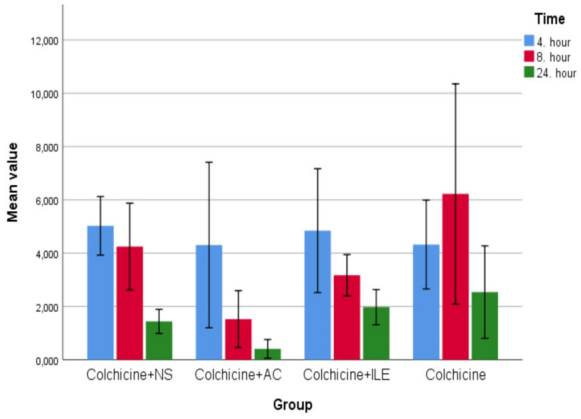

Figure 1a: Changes in colchicine levels in groups at 4th, 8th and 24th hr.

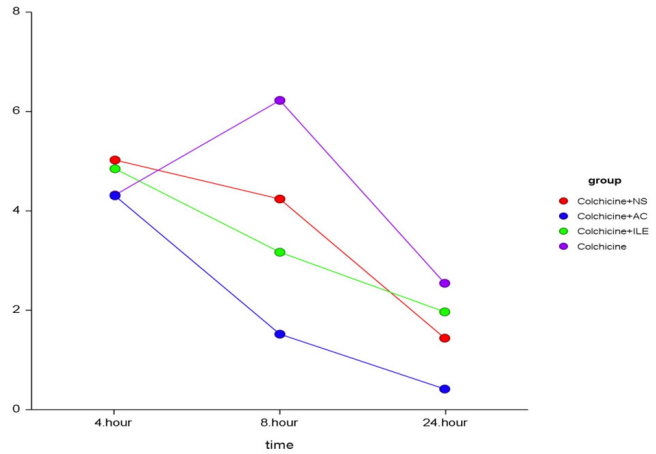

Figure 1b: Changes in colchicine levels in groups at 4th, 8th and 24th hr.

the groups at the 8th hr was found to be statistically significant (p=0.004) (Table).

It was determined that the significant difference between the groups at the 8th hr was between Group 2 (Colchicine group given AC) and Group 4 (Colchicine group not treated) (p=0.003, Mann-Whitney U, Bonferroni correction).

Blood Colchicine levels decreased in all groups in blood samples taken at 24 hr (with and without treatment).

Compared to the blood colchicine level at the 8th hr, the blood colchicine level at the 24th hr decreased the most in the 4th group (2.8075 ng/mL) given no treatment, followed by the 1st group (2.8075 ng/mL) given NS and the 3rd group given ILE group (1.9634 ng/mL) and group 2 (1.11583 ng/mL) given AC followed. Compared to the 8th hr, blood colchicine levels at 24 hr decreased by 66.1% in the NS group, decreased by 73.12% in the AC group and decreased by 37.73% in the ILE group. The blood colchicine level in the 4th group, which was not treated, decreased by 59.17% (1,89867 ng/mL) at the 24th hr compared to the 8th hr. A statistically significant difference was found between the colchicine levels in the blood samples taken at the 24th hr (p=0.003) (Table).

Significant difference between the groups at the 24th hr was detected between Group 2 (Colchicine group given AC) and Group 4 (Colchicine group not treated) (p=0.009, Mann-Whitney U, Bonferroni correction).

The change in colchicine level over time in Group 1 (Colchicine+NS) was also found to be statistically significant (p=0.006). It was determined that the significant difference between the groups was between 4 hr and 24 hr (p=0.04, Wilcoxon test, Bonferroni correction) (Table 3).

Table 3: Colchicine levels change at 4, 8 and 24 hr of each group.

		4 hr (ng/mL)	8 hr (ng/mL)	24 hr (ng/mL)
Group 1 (Colchicine+NS)	Mean±SD	5.0253±1.04553	4.2468±1.55071	1.4393±0.43240
	Median	4.8995	3.5880	1.5820
	Min-Max	3.66-6.61	2.97-6.92	0.79-1.83
	Difference	+4.59163	-0.7785	-3.586
	p*	0.006		
Group 2 (Colchicine+AC)	Mean±SD	4.3045±2.95911	1.5258±1.01761	0.4100±0.33360
	Median	4.5610	1.3075	0.2820
	Min-Max	0.10-8.67	0.61-3.47	0.14-1.03
	Difference	+3.75067	-2.7787	-3.8945
	p*	0.030		
Group 3 (Colchicine+ILE)	Mean±SD	4.8457±2.21482	3.1707±0.73792	1.9743±0.62981
	Median	4.7035	3.1495	2.0555
	Min-Max	2.35-8.16	2.28-4.08	1.13-2.70
	Difference	+4.4602	-1.675	-2.8714
	p*	0.016		
Group 4 (Colchicine)	Mean±SD	4.3233±1.58798	6.2220±3.93786	2.5402±1.65154
	Median	4.1475	4.2640	1.6145
	Min-Max	2.87-6.56	3.59-13.43	1.19-4.71
	Difference	+3.99363	+1.8987	-2.5402
	p*	0.030		

NS: Normal Saline**; ILE:** Intravenous Lipid Emulsion; **AC:** Activated Charcoal; **Min:** Minimum; **Max:** Maximum; Friedman testi* $p<0.05$.

The change in colchicine level over time in Group 2 (Colchicine+AC) was found to be statistically significant ($p=0.015$). It was determined that the significant difference between the groups was between 4 hr and 24 hr ($p=0.28$, Wilcoxon test, Bonferroni correction) (Table 3).

The change in colchicine level over time in Group 3 (Colchicine+ILE) was found to be statistically significant ($p=0.001$). It was determined that the significant difference between the groups was between 4 hr and 24 hr ($p=0.012$, Wilcoxon test, Bonferroni correction). (Table 3).

The change in colchicine level in Group 4 (Colchicine) over time was found to be statistically significant ($p=0.001$). It was determined that the significant difference between the groups was between 8 hr and 24 hr ($p=0.028$, Wilcoxon test, Bonferroni correction). (Table 3).

The 4 hr, 8 hr and 24 hr changes of colchicine levels in the groups are shown in Figure 1a,1b. In all treatment groups (Group 1, 2 and 3), statistically significant decreases were found in blood colchicine levels with increasing time. ($p<0.005$).

The blood colchicine level was the lowest in all groups at the 24th hr. Two-way Friedman test was used to evaluate time and group interaction. Accordingly, time and group interaction were not statistically significant ($p=0.091$).

DISCUSSION

Colchicine is a drug used in the treatment of gout attacks and Familial Mediterranean Fever. High doses (>0.8 mg/kg) of colchicine result in major toxicity and mortality.[3,5,7,8,38-40]

The amount of drug taken and the severity of clinical findings and prognosis were not found to be directly proportional.[7,8] Chromatography is recommended for the detection of colchicine in body fluids (such as serum, urine, milk) and tissues due to its rapid distribution and lability in the body.[9-16]

Differences in the level of colchicine in body fluids and tissues have been reported in humans. In a case report involving suicide by ingestion of colchicine tablets, a plasma concentration of 4.5 ng/mL was found 24 hr after ingestion.[39] In another study, the level of colchicine in the peripheral blood for fatal overdose was reported as 29 ng/mL.[41] In a study showing the change in colchicine level over time, it was reported that in a 39-year-old woman with colchicine overdose, the colchicine blood concentration was 250 microgram/L 2 hr after ingestion, but no drug could be detected in the chromatographic measurement of the patient who died 40 hr after colchicine ingestion.[40]

Unfortunately, there is still no effective treatment method other than supportive treatment in colchicine intoxication, which has a high mortality.

In studies, it was emphasized that the effects of treatments such as oral AC or hemodialysis were insufficient in colchicine intoxications.[6,17-20] On the other hand, in an experimental study investigating the efficacy of AC to colchicine, colchicine could not be detected from both gastric and intestinal media after 50 g AC was administered (<0.1 µg/mL). The *in vitro* binding of colchicine to AC suggests that AC should be administered for decontamination of patients in emergency depertment admissions with colchicine overdose.[42]

In our experimental study, the lowest mean blood colchicine level at the 4th, 8th and 24th hr was in the AC group. This study showed that AC should be the first treatment method that should be used in colchicine overdose absolutely and without losing time.

There are studies showing that ILE is effective in both LAs toxicity and other drug toxicities other than LA.[22-37] In a 2010 study evaluating 23 animal and 50 human studies involving the use of ILE in intoxications, ILE was also found to have some benefits against poisoning with bupivacaine, verapamil, chlorpromazine, some tricyclic antidepressants and beta-blockers.[26] Tebbut *et al.*'s study demonstrated the benefits of ILE over Normal saline in verapamil toxicity.[32] In both rat and rabbit models, ILE has been shown to reduce propranolol-induced QRS prolongation and bradycardia.[35,36] ILE has also been used for other toxicities, including herbicides and pesticides.[43] ILE has also been used in overdose of antidepressants in experimental studies.[44-46] Toxicity of haloperidol treated with ILE has been reported.[22]

Whether ILE has an effect on colchicine intoxication has not been investigated to date.

In this experimental study, the effect of colchicine on blood levels was investigated by giving ILE to experimental animals given colchicine. In this study, statistically significant reductions in mean colchicine levels were detected in animals given ILE over time. In this study, the effect of ILE on colchine blood levels was compared with Normal Saline and Activated charcoal, which are used as standard supportive treatment in intoxications. In this study, ILE was found to be as effective as AC and NS in reducing colchicine blood levels.

In our study, all three treatment methods (NS, AC and ILE) were found to be effective in reducing blood colchicine levels both at the 8th and 24th hr. NS and AC treatments are among the treatment methods recommended in the literature for both general drug intoxication management and colchicine intoxication. However, there is no study to date on whether ILE treatment is effective in colchicine intoxications.

In this experimental study, ILE treatment was found to be effective in lowering blood Colchicine levels. While AC application was found to be the most effective treatment method in reducing blood colchicine level, it was determined that both NS and ILE application could be used in colchicine intoxications.

In our experimental study, we tested each of the three treatment methods (AC, NS and ILE) separately and showed that each of them was effective in lowering blood Colchicine levels. Considering that colchicine is a drug with labile distribution, there is a need for further studies in which all three treatments (AC, NS and ILE) are used together and its distribution at the blood and barber tissue level.

CONCLUSION

In this experimental study, it has been shown that AC application is quite effective in reducing blood colchicine levels and ILE application is also effective in reducing blood colchicine levels as well as NS and AC. It can be used as an early treatment option in ILE, colchicine overdoses, together with supportive treatments such as NS and AC. Tissue-level studies are needed to better demonstrate the efficacy of ILE in colchicine overdose. However, further studies are needed for more effective methods in the treatment of colchicine overdose.

LIMITATIONS

This experimental study is one of the first studies to test the efficacy of ILE (Intravenous Lipid Emulsion) in the overdose of colchicine, which is one of the deadly intoxication drugs and has not yet found a definitive treatment. Considering the labile distribution of colchicine in tissues, further studies are needed at the tissue level.

ACKNOWLEDGEMENT

We respectfully commemorate our pediatrician friend, associate professor Suat Bicer, who lost due to the colchicine overdose that led to the emergence of this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors (MFC, SS, DNO, FC, ES, EÇK, DSMC) participated sufficiently in this project to take responsibility for its content and all authors approved the manuscript.

ETHICS APPROVAL

This experimental study was conducted after obtaining approval from Yeditepe University Animal Research local ethics committee (number: 632; date of decision: 22.12.2017). It was carried out at Yeditepe University Faculty of Medicine Experimental Research Center.

ABBREVIATIONS

NS: Normal Saline; **ILE:** Intravenous Lipid Emulsion; **AC:** Activated Charcoal; **Min:** Minimum; **Max:** Maximum; **LA:** Local Anesthetics.

SUMMARY

Although colchicine intoxication with a narrow therapeutic index is rare, its potentially life-threatening risk is high. Whether ILE has an effect on colchicine intoxication has not been investigated to date. In this experimental study, ILE treatment was found to be effective in lowering blood Colchicine levels. While AC application was found to be the most effective treatment method in reducing blood colchicine level, it was determined that both NS and ILE application could be used in colchicine intoxications.

REFERENCES

1. M. Rochdi, A. Sabouraud, C. Girre, R. Venet, J.M. Scherrmann, Pharmacokinetics and absolute bioavailability of colchicine after IV and oral administration in healthy human volunteers and elderly subjects, Eur. J. Clin. Pharmacol. 1994;46(4):351-4.
2. Wallace SL, Omokoku B, Ertel NH. Colchicine plasma levels. Implications as to pharmacology and mechanism of action, Am. J. Med. 1970;48(10):443-8.
3. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2009 Annual Report of the American Association of Poison Control Centers'National Poison Data System (NPDS): 27th Annual Report. Clin Toxical 2010;48:979-1178.
4. Ozdemir R, Bayrakci B, Teksam O. Fatal poisoning in children: Acute Colchicine intoxication and new treatment approaches. Clinical Toxicology. 2011;49(8):739-43.
5. Gür Güven A, Bahat E, Akman S, Artan S, Erol M. "Late diagnosis of severe colchicine intoxication." Pediatrics. 2002;109(5):971-3.
6. Finkelstein Y, Aks SE, Hutson JR, Juurlink DN, Nguyen P, Dubnov-Raz G, *et al.* Colchicine poisoning: the dark side of an ancient drug. Clin Toxicol (Phila). 2010;48(5):407-14.
7. Bismuth C, Baud F, Dally S. Standardized prognosis evaluation in acute toxicology: Its benefit in colchicine, paraquat and digitalis poisonings. J Toxicol Clin Exp 1986;6(1):33-8.
8. Weakley-Jones B, Gerber JE, Biggs G. Colchicine poisoning: Case report of two homicides. Am J Forensic Med Pathol 2001;22(2):203-6.
9. Jiang Y, Wang J, Wang Y, Li H, Fawcett JP, Gu J. Rapid and sensitive liquid chromatography-tandem mass spectrometry method for the quantitation of colchicine in human plasma. J Chromatogr B Analyt Technol Biomed Life Sci. 2007;850(1-2):564-8.
10. Thompson RD. Liquid chromatographic determination of colchicine in pharmaceuticals: collaborative study. J Assoc Off Anal Chem. 1985;68(5):1051-5.
11. Chen QH, Hou S, Gan LC, Li YB, Song X, Cai Z. Determination of colchicine in mouse plasma by high performance liquid-chromatographic method with UV detection and its application to pharmacokinetic studies. Yakugaku Zasshi. 2007;127(9):1485-90.
12. Lacey E, Brady RL. Separation of colchicine and related hydrolysis and photodecomposition products by high-performance liquid chromatography, using copper ion complexation. J Chromatogr. 1984;315:233-41.
13. Hamscher G, Priess B, Nau H, Panariti E. Determination of colchicine residues in sheep serum and milk using high-performance liquid chromatography combined with electrospray ionization ion trap tandem mass spectrometry. Anal Chem. 2005;77(8):2421-5.
14. Watterson JH, Imfeld AB, Cornthwaite HC. Determination of colchicine and O-demethylated metabolites in decomposed skeletal tissues by microwave assisted extraction, microplate solid phase extraction and ultra-high performance liquid chromatography (MAE-MPSPE-UHPLC). J Chromatogr B Analyt Technol Biomed Life Sci. 2014;960:145-50.
15. Ko RJ, Li WY, Koda RT. Determination of the antimitotic agents N-desacetylcolchicine, demecolcine and colchicine in serum and urine. J Chromatogr. 1990;525(2):411-8.
16. Tracqui A, Kintz P, Ludes B, Rougé C, Douibi H, Mangin P. High-performance liquid chromatography coupled to ion spray mass spectrometry for the determination of colchicine at ppb levels in human biofluids. J Chromatogr B Biomed Appl. 1996;675(2):235-42.
17. Hood RL. Colchicine poisoning. J Emerg Med. 1994;12(2):171-7.
18. Peake PW, Pianta TJ, Succar L, Fernando M, Buckley NA, Endre ZH. Fab fragments of ovine antibody to colchicine enhance its clearance in the rat. Clinical Toxicology. 2015;53(5):427-32.
19. Baud FJ, Sabouraud A, Vicaut E, Taboulet P, Lang J, Bismuth C, *et al.* Treatment of severe colchicine overdose with colchicine-specific Fab fragments, N. Engl. J. Med.1995;332(10): 642-5.
20. Fabresse N, Allarda J, Sardabya M, Thompsonc A, Cluttond RE, Eddlestonc M, *et al.* LC-MS/MS quantification of free and Fab-bound colchicine in plasma, urine and organs following colchicine administration and colchicine-specific Fab fragments treatment in Göttingen minipigs. Journal of Chromatography B. 2017;1060:400-6.
21. Gosselin S, Hoegberg LC, Hoffman RS, Graudins A, Stork CM, Thomas SH, *et al.* Evidence-based recommendations on the use of intravenous lipid emulsion therapy in poisoning.Clin Toxicol (Phila). 2016;54(10):899-923.
22. Weinberg GL, Laurito CE, Geldner P, Pygon BH, Burton BK. Malignant ventricular dysrhythmias in a patient with isovaleric acidemia receiving general and local anesthesia for suction lipectomy. J Clin Anesth. 1997;9(8):668-70.
23. Lam SHF, Majlesi N, Vilke GM. Use of intravenous fat emulsion in the emergency department for the critically ill poisoned patient. J Emerg Med 2016;51(2):203-14.
24. Fettiplace MR, McCabe DJ. Lipid emulsion improves survival in animal models of local anesthetic toxicity: a meta-analysis. Clin Toxicol (Phila). 2017;55(7):617-23.
25. Karcioglu O. Use of lipid emulsion therapy in local anesthetic overdose. Saudi Med J. 2017;38(10):985-93.
26. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin Toxicol (Phila). 2010;48(1):1-27.
27. Sirianni AJ, Osterhoudt KC, Calello DP, Muller AA, Waterhouse MR, Goodkin MB, *et al*: Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. Ann Emerg Med. 2008;51(4):412-5.
28. Weinberg G, Di Gregorio G, Hiller D, Hewett A, Sirianni A. Reversal of haloperidol-induced cardiac arrest by using lipid emulsion. Ann Intern Med. 2009;150(10):737-8.
29. Rothschild L, Bern S, Oswald S, Weinberg G. Intravenous lipid emulsion in clinical toxicology. Scand J Trauma Resusc Emerg Med. 2010;18:51
30. Han SK, Jeong J, Yeom S, Ryu J, Park S. Use of a lipid emulsion in a patient with refractory hypotension caused by glyphosate-surfactant herbicide. Clin Toxicol (Phila) 2010;48(6):566-8.
31. Agarwala R, Ahmed SZ, Wiegand TJ. Prolonged use of intravenous lipid emulsion in a severe tricyclic antidepressant overdose. J Med Toxicol. 2014;10(2):210-4.
32. Tebbutt S, Harvey M, Nicholson T, Cave G. Intralipid prolongs survival in a rat model of verapamil toxicity. Acad Emerg Med. 2006;13(2):134-9.
33. Young AC, Velez LI, Kleinschmidt KC. Intravenous fat emulsion therapy for intentional sustainedrelease verapamil overdose. Resuscitation. 2009;80(5):591-3.
34. Macala KF, Khadaroo RG, Panahi S, Gragasin FS, Bourque SL. Low dose Intralipid resuscitation improves survival compared to ClinOleic in propranolol overdose in rats. PLoS One. 2018;13(8):e0202871.
35. Cave G, Harvey M. Lipid emulsion may augment early blood pressure recovery in a rabbit model of atenolol toxicity. J Med Toxicol. 2009;5(1):50.
36. Harchelroad F, Palma A: Efficacy and safety of intravenous lipid therapy in a B-blocker overdose. Clin Toxicol (Phila). 2008;46:620
37. Yurtlu BS, Özbilgin Ş, Yurtlu DA, Boztaş N, Kamacı G, Akaltun M, *et al.* Intravenous lipid emulsion prolongs survival in rats intoxicated with digoxin. Am J Emerg Med. 2016;34(6):1112-6.
38. Kicka M, Olszowy Z, Jankowski Z, Celiński R, Kłopotowski T, Bazylewicz A, *et al.* Fatal colchicine poisoning--case report and review of literature. Przegl Lek. 2010;67(8):630-2.
39. Dehon B, Chagnon JL, Vinner E, Pommery J, Mathieu D, Lhermitte M. Colchicine poisoning: report of a fatal case with body fluid and post-mortem tissue analysis by high-performance liquid chromatography.Biomed Chromatogr.1999;13(3): 235-8.
40. Caplan YH, Orloff KG, Thompson BC. A fatal overdose with colchicine. J Anal Toxicol. 1980;4(3):153-5.
41. Lauer E, Widmer C, Versace F, Staub C, Mangin P, Sabatasso S, *et al.* Body fluid and tissue analysis using filter paper sampling support prior to LC-MS/MS: application to fatal overdose with colchicine. Drug Test Anal. 2013;5(9-10):763-72.

42. Zawahir S, Gawarammana I, Dargan PI, Abdulghni M, Dawson AH. Activated charcoal significantly reduces the amount of colchicine released from Gloriosa superba in simulated gastric and intestinal media. Clin Toxicol (Phila). 2017;55(8):914-8.
43. Crandell D, Weinberg GL: Moxidectin toxicosis in a puppy successfully treated with intravenous lipids. Journal of Veterminary Emergency and Critical Care 2009;19(2):181-6.
44. Hawton K, Bergen H, Simkin S, *et al.* Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry. 2010;196(5):354-8.
45. Harvey M, Cave G. Intralipid outperforms sodium bicarbonate in a rabbit model of clomipramine toxicity. Ann Emerg Med. 2007;49(2):178-85.
46. Harvey M, Cave G, Hoggett K. Correlation of plasma and peritoneal diasylate clomipramine concentration with hemodynamic recovery after intralipid infusion in rabbits. Acad Emerg Med. 2009;16(2):151-6.

Cite this article: Çelikmen MF, Sarikaya S, Özüçelik DN, Canbolat F, Sümer E, Keleş EÇ, *et al*. Comparison of Normal saline, Activated Charcoal and Intravenous Lipid Emulsion in a Rat Model of Colchicine Overdose: Experimental Study. Indian J of Pharmaceutical Education and Research. 2024;58(3):794-801.