Factors Associated With the Occurrence of Adverse Effects Resulting From Hypodermoclysis in Older Adults in Palliative Care: A Cohort Study

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ABSTRACT

This study aimed to analyze the factors associated with local adverse effects resulting from hypodermoclysis in older adult patients in palliative care. The study involved 127 older adults undergoing palliative care at a hospital in southeastern Brazil. Data collection was performed from August to November 2019. Patients aged 60 years or older, with a prescription for hypodermoclysis at the time of admission and who were not receiving hypodermoclysis at the time of admission, were included. Data collected included sociodemographic, clinical, pharmacotherapeutic, and adverse effects of hypodermoclysis administration. Most participants were women (59.0%), with a mean age of 78.5 years. Frailty was the most prevalent diagnosis (26.8%), and 80.2% of patients were in the end-of-life stage. There was an incidence of 24.0% of adverse events, with catheter obstruction and swelling in the surrounding area of the hypodermoclysis site being the most frequent at 11.3% and 8.5%, respectively. Ondansetron administration by hypodermoclysis was 3 times more likely to have an adverse effect compared to not using this drug. In contrast, a protective factor was evident with the administration of 0.9% sodium chloride, which contributed to the reduction of complications. The occurrence of adverse effects from hypodermoclysis in the study population of older adults in palliative care was low.

Key words: infusions, injection site reaction, nursing care, subcutaneous

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BACKGROUND

Hypodermoclysis is the subcutaneous administration of isotonic solutions and medications. It is an alternative therapy used in clinical and palliative care of the older adult, in which patients have health conditions that make it impossible to maintain adequate hydration, nutrition, and symptom control. Thus, hypodermoclysis can be considered the route for replacing fluids, electrolytes, and some drugs.[1,2]

Several factors can influence absorption in the subcutaneous space, including the size of the molecules being infused, the thickness of the subcutaneous tissue, and the pH of the drug or solution.[1,3] Intrinsic factors to the patient, such as vasoconstriction, hypoperfusion, and capillary atrophy (consequences of diseases that affect older adult patients and in the end-of-life stage), can interfere in the absorption process.[1,4] However, the literature has shown that hypodermoclysis is safe and has numerous advantages over other parenteral routes, particularly in older adult patients.[5,6]

Although hypodermoclysis is an effective and safe procedure, adverse events may occur at the catheter insertion site. The incidence rate of local adverse effects varies depending on the study populations, contexts, and methodologies used. The following adverse effects stand out in the older adult population: (1) edema between 1.7% and 22.0%,[7-9] (2) erythema between 1.7 and 8.5%,[8,10] (3) cellulitis at 2.9%,[9] and (4) hyperemia at 9.1%.[7,11] Catheter occlusion and extravasation at the insertion site are also mentioned in the literature; however, the rates were not reported.[12]

A recent systematic review study and meta-analysis reviewed available original publications on the harms and benefits of subcutaneous hydration in older patients. Hypodermoclysis for hydration treatment showed an incidence of 90 adverse events per 1000 infusions (subcutaneously) versus 130 adverse events per 1000 infusions (intravenously; 95% confidence interval [CI], 102–169). The most reported adverse effects per 1000 subcutaneous infusions were as follows: local edema between 25 and 41, hematoma between 16 and 29, pain between 9 and 19, need to restart the infusion between 3 and 9, extravasation between 1 and 6, pruritus between 1 and 5, and accidental removal of the catheter between 0 and 5.[5] Therefore, in the context of nursing care, it is necessary to understand the factors associated with local adverse effects resulting from hypodermoclysis to promote this administration route and enable interventions and prevention measures aimed at improving the quality of care for patients under palliative care, in addition to reducing the expenses arising from the use of other administration routes in the treatment of the patient.

In view of the above, this study aimed to analyze the factors associated with local adverse effects resulting from hypodermoclysis in older adult patients under palliative care.

METHODS

Study Design

This is a concurrent cohort study involving older adult patients under palliative care. The study was carried out in a palliative care unit of a reference university hospital for a metropolitan region in southeastern Brazil.

Patient Selection

The minimum sample size of 127 patients was calculated according to Hsieh,[13] considering the study objective and the multiple logistic regression analysis. Whittemore's formula[14] was used considering a significance level of 5%, power of 90%, and an average effect size (0.50), which is equivalent to an odds ratio of 2.5, while the multiple correlation coefficient was 0.50 and the occurrence of adverse effects was 25%.[13,14] The data collection period was from August to November 2019, and the study participants were selected by nonprobability convenience sampling.

The inclusion criteria for patients in the study were as follows: age equal to or greater than 60 years (according to the definition of older adults/elderly proposed by the United Nations for developing countries),[15] prescription of hypodermoclysis at the admission time, patients who were not receiving hypodermoclysis at the admission time, and patients who were able to read health care literature. All patients were considered able to answer the questions, as they were conscious and presented sound faculties, as assessed using the Glasgow Coma Scale. No exclusion criteria were adopted.

The present study was approved by the Federal University of Minas Gerais Research Ethics Committee under opinion No. 2371718.9.0000.5149. All stages of the study were based on Resolution 466 of 2012-National Health Council for Scientific Research in Human Beings.

Data Collection

Sociodemographic, clinical, and pharmacotherapeutic data were obtained directly from the medical record and from the patient and/or responsible family member through the application of a structured questionnaire, developed by the researchers of this study. Data were processed with double-independent typing and in electronic spreadsheets in the Excel (Microsoft, Redmond, WA) software, which were later compared, with the purpose of eliminating the possibility of typing errors.

The outcome variable of the study was the occurrence of a local adverse effect resulting from hypodermoclysis. The definitions of the adverse effects identified in the present study are presented in Table 1. It is noteworthy that the pain variable was self-reported by the patients and the other variables were measured by the researcher.

The subcutaneous catheter used was a Teflon cannula and was inserted by the unit nurse using a technique based on the Manual of the Brazilian Society of Geriatrics and Gerontology 2017.[1] In addition, the nurse researcher

TABLE 1

Concepts of Variables Related to Adverse Effects Resulting From Hypodermoclysis

Variable	Concept	Measure
Pain	Unpleasant sensation, variable in intensity and extent of localization produced by the stimulation of nerve endings specialized in its reception.[16]	Self-reported/Presence/absence
Edema	Edema in and around the insertion site, which increases in area above 10 cm[17] and when there was no decrease after 4 hours after decreasing the infusion volume, as recommended by the SBGG.[1]	Presence/absence
Erythema	Erythema is caused by capillary vasodilation and appears as a change in skin color with a reddish tone. As recommended by the SBGG, wait 4 hours for symptom onset, and consider it as erythema if there is no resolution.[1,17]	Presence/absence
Cellulitis	Cellulitis occurs when fluid extravasation is identified at the catheter insertion site.[17]	Presence/absence
Skin hardening	Identification of a nonpalpable region in an area of up to 10 cm at the hypodermoclysis site.[17]	Presence/absence
Hematoma	*Hematoma* is defined as an accumulation of blood in an organ or tissue. In the case of subcutaneous tissue, it presents as a change in color from red to purple to yellow.[17]	Presence/absence
Necrosis	Considered as cell death of a tissue or organ, necrosis will be considered cell death, which causes loss of viable tissue.[17]	Presence/absence
Occlusion	Poor absorption in the subcutaneous tissue, preventing the continuity of the infusion of fluids or medications.[18]	Presence/absence
Hypersensitivity	Overreaction of the immune system to a substance perceived as foreign to the body.[19]	Presence/absence

Abbreviation: SBGG, Sociedade Brasileira de Geriatria e Gerontologia.

adopted the following system to identify adverse effects: initial assessment (first day of insertion, D1) to verify that the outcome variable was not present. Assessment of the hypodermoclysis insertion site was performed every 24 hours until an event occurred (D2, D3, etc), discharge, or death, with no interruptions due to holidays. The assessment of adverse effects at the catheter insertion site was performed by the nurse researcher. The period for verifying the insertion site was determined considering the operational feasibility, adopting an interval of 24 hours due to the lack of studies that justify the time in which the adverse effects appear. It is worth mentioning that a previous study carried out in Brazil by Guedes et al[11] also performed daily observation.

The following explanatory variables were recorded in the structured form as described here. The first variables were sociodemographic: sex (male and female) and age in years. Second were clinical comorbidities (nominal variable), prognosis, and patient functionality using the current Palliative Performance Scale (PPS), classified as stable, end-of-life, and transitional phase.[20] The Clinical Frailty Scale (CFS) was also used and divided into 3 categories: not frail (CFS 1-4), mild-to-moderately frail (CFS 5-6), and severely frail (CFS 7-8). Body mass index (BMI) was adapted for the older adult population as follows: low weight, <22.0 kg/m^2; eutrophic, 22.0 to 26.9 kg/m^2; overweight, 27.0 to 29.9 kg/m^2; and obese, ≥ 30.00 kg/m^2. Also included in this variable was subcutaneous fold (in millimeters); insertion site (abdomen, deltoid, infrascapular, subclavicular, and vastus lateralis of the thigh), infusion rate (in milliliters per hour), and type of infusion (continuous infusion pump, bolus, gravity). The final variable was pharmacotherapeutic, including hydration solution (5% glucose, 0.9% sodium chloride) and drug name.

Statistical Analysis

Patients (n = 127) were considered as the unit of analysis for the inferential statistical analysis of sociodemographic and clinical variables. In addition, insertions were considered as the unit of analysis (n = 177) for the pharmacotherapeutic variables and those related to hypodermoclysis, since the same patient may receive more than 1 hypodermoclysis procedure. Descriptive analyses of categorical variables were performed by determining absolute and relative frequencies, as well as measures of position, central tendency, and dispersion for quantitative variables.

The nonparametric Mann-Whitney, χ^2, and Fisher exact tests were used to verify the association between the occurrence or not of adverse effects resulting from hypodermoclysis and the sociodemographic, clinical, and pharmacotherapeutic variables, observing the premises of the tests and the characteristics of the explanatory variables. Then, the stepwise method was implemented to select the variables to be used in the multiple logistic regression. Variables with a P value <0.2 were selected for multiple logistic regression.

With the complete model fitted, the variance inflation factors (VIF) were calculated to identify possible multicollinearity problems, and the backward method was then applied after removing the variables that presented problems; this involves removing the variable with the highest *P* value one at a time, repeating the procedure until only significant variables remain in the model. A significance level of 5% was adopted for the backward method.

The Hosmer-Lemeshow test[21] and the pseudo R^2 of Nagelkerke[22] were used to assess the quality of fit of the logistic model, which represents how much the model explains the variation in the presence of adverse effects, the area under the receptor operating characteristic (ROC) curve, called the area under the ROC curve,[23] and the simulation envelope.[24] Statistical analyses were performed using the R software program (version 3.6.0; R: The R Project for Statistical Computing, https://www.r-project.org).

RESULTS

The study included 127 older adults who underwent 177 hypodermoclysis procedures. A total of 75 of the 127 older adults included in the study were women. Frailty was the most prevalent diagnosis in 34 elderly people and was evaluated according to the CFS. According to the PPS, 101 patients were in the end-of-life stage. Anthropometric data could be obtained for only 79 older adults, and the BMI classified 32 of these older adults as being low weight or eutrophic. The predominant insertion site was the vastus lateralis of the thigh for 101 hypodermoclysis procedures (Table 2).

There was an incidence of 24% adverse events, with catheter obstruction and edema being the most frequent, at 11.3% and 8.5%, respectively. In addition, BMI ($P = .065$) was statistically significant ($P < .20$) in being

TABLE 2

Association of Clinical and Sociodemographic Independent Variables With Adverse Events Resulting From Hypodermoclysis (n = 127): Univariate Analysis

Variable	Categories	Adverse Events				*P* Value*
		No		Yes		
		n	%	n	%	
Sex	Female	58	77.3	17	22.7	.761
	Male	39	75.0	13	25.0	
Comorbidities	Frailty	26	76.5	08	23.5	.765
	Dementia	21	75.0	07	25.0	
	Neurological diseases	10	62.5	06	37.5	
	Neoplasm	22	84.6	04	15,4	
	Cardiovascular diseases	06	75.0	02	25.0	
	COPD	2	100	-	-	
	Others	10	73.9	03	23.1	
Current PPS	End-of-life stage	75	74.3	26	25.7	.469
	Transitional	20	83.3	04	16.7	
	Stable	02	1.5	-	-	
BMI	Low weight	29	90.6	03	9.4	**.065**
	Eutrophic	22	68.8	10	31,3	
	Overweight	06	100.0	-	-	
	Obese	06	66.7	03	33.3	
Insertion site	Abdomen	12	26.67	33	73.33	.713
	Deltoid	6	27.27	16	72.73	
	Infrascapular	-	-	5	100.00	
	Subclavicular	-	-	4	100.00	
	Vastus lateralis of the thigh	24	23.76	77	76.24	

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; PPS, Palliative Performance Scale.
*χ^2 test. *P* values in bold are significant.

associated with the occurrence of adverse effects resulting from hypodermoclysis among the categorical clinical and sociodemographic variables (Table 2).

A total of 317 drugs were administered to the participants of the present study, with dypirone being the most frequent drug (23.30%), and 0.9% sodium chloride the most used solution (61.25%; Table 3). It was identified that sodium chloride ($P = .013$), methadone ($P = .001$), butylscopolamine bromide ($P = .194$), dexamethasone ($P = .083$), ondansetron ($P = .036$), midazolam ($P = .019$), and ocreotide ($P = .092$) obtained values lower than .20 by univariate analysis, as shown in Table 3.

It was not possible to obtain measurements for all patients for numerical variables such as BMI, arm circumference, and calf circumference. The following averages were found for the patients who had complications: mean arm circumference was 28.05 cm, calf circumference 32.33 cm, subcutaneous fold 22.86 mm, length of stay 3.62 days, total medication dose 3.33 mL, infusion volume 258.26 mL/h, and infusion rate 32.13 mL/h (Table 4).

The Mann-Whitney test identified that 8 numerical variables were significantly associated ($P < .20$) with adverse effects resulting from hypodermoclysis, namely: BMI ($P = .074$), arm circumference ($P = .04$), calf circumference ($P = .062$), subcutaneous fold ($P = .02$), length of stay ($P = .074$), medication dose ($P = .117$), infusion volume ($P = .087$), and gravity infusion ($P = .006$), according to Table 4.

Variables for which the *P* value was ≤.20 in Tables 2, 3, and 4 were selected for the multivariate model. The final multiple logistic regression model is presented in Table 5, where it can be identified that the drug ondansetron ($P = .006$) was significantly associated with the presence of adverse effects ($P < .05$), and sodium chloride ($P = .003$) was a protector factor for the studied sample (range, 0.15–0.67).

Ondansetron administration by hypodermoclysis can be 3 times more likely to have an adverse effect compared with not using this drug (odds ratio [OR] = 3.16 [95% CI, 1.38–7.24]). It was identified that, of the 15 adverse effects related to ondansetron, catheter occlusion and edema were the most frequent adverse effects (53.3% and 40.0%, respectively). On the other hand, there is evidence of a protective effect of 0.9% sodium chloride (OR = 0.31 [95% CI, 0.15–0.67]; Table 5).

The value of the area under the ROC curve was 0.663, VIF was 1.11, Hosmer-Lemeshow test *P* value was 1.00, pseudo R^2 was 11.5%, and the simulated residuals were within the limits of the envelope: 1.69% of the points were outside the envelope. These values show that the logistic model is adequate.

DISCUSSION

In the context of palliative care, this study sought to identify the factors associated with the occurrence of adverse events from the subcutaneous administration route. Thus, the data show a low occurrence of adverse events resulting from hypodermoclysis in the study population of older adult patients, in line with the results reported by Danielsen et al.[5] A Brazilian study that characterized the complications associated with the use of the subcutaneous route for infusion drugs and solutions in palliative care included people over 18 years of age, but with a predominance of 87.3% of older adults, there was an occurrence frequency of 36.4% of adverse events. It is noteworthy that occlusion and edema were the most frequent adverse events.[11] International studies cite edema as the most frequent adverse effect (1.7% to 22.0%).[7-9] However, occlusion is reported in studies with no data record.[12,25]

A meta-analysis study showed that the administration of 0.9% sodium chloride for subcutaneous hydration in older adults is safe; the authors of this study attributed a moderate level of evidence by the Grading of Recommendations Assessment, Development and Evaluation.[5]

The results of the present study showed a protective effect of 0.9% sodium chloride, which is in line with systematic review studies and clinical trials published to date.[26] It is also worth noting that the isotonicity and pH of sodium chloride meet the recommendations for administration by hypodermoclysis.[26]

The use of subcutaneous antiemetics has been identified and described in several publications.[7,27-30] However, in this study, the chance of experiencing adverse effects with the use of ondansetron was greater. Ondansetron is a drug that has antiemetic activity, being widely used in palliative care services in Brazil and included in institutional protocols.[1] The subcutaneous administration of this drug is off-label, meaning that it is not included within the list of drugs registered in Brazil.[1] Ondansetron was administered by intermittent gravity infusion in the patients of this study, which raises doubts about the volume for infusion, compatibility, infusion time, and administration form. Ondansetron was administered by gravity infusion and intermittently in the patients of this study.

Solutions and medications to be used for hypodermoclysis must have a pH close to neutral or normal (7.38-7.45). The administration of drugs with extreme pH (<2 or >11) by hypodermoclysis is not recommended because they present a risk for precipitation or local irritation.[30-33] The pH of ondansetron is between 3.3 and 4.0. This acidity may have influenced the occurrence of adverse effects in this cohort. Although this drug has an acidic pH, it can be administered subcutaneously, provided it is given slowly.[34,35]

The authors of a systematic review study that aimed to propose a list of drugs, diluents, and dilution volume identified that there is no consensus for use in hypodermoclysis. The authors subsequently invited specialists in the field of palliative care, nursing, medicine, and clinical pharmacy to propose specific recommendations related to the infusion

TABLE 3

Association of Pharmacotherapeutic Variables With Adverse Events Resulting From Hypodermoclysis (n = 177 Punctures): Univariate Analysis

		Adverse Events				
		No		Yes		
Medication		N	%	N	%	*P* Value*
Sodium chloride	No	53	67.09	26	32.91	**.013**
	Yes	82	83.67	16	16.33	
50% glucose	No	115	76.67	35	23.33	.807
	Yes	20	74.07	7	25.93	
Ceftriaxone	No	123	77.36	36	22.64	.380
	Yes	12	66.67	6	33.33	
Meropenem	No	129	76.33	40	23.67	1.000
	Yes	6	75.00	2	25.00	
Butylescopolamine Bromide	No	120	77.92	34	22.08	.194
	Yes	15	65.22	8	34.78	
Metoclopramide	No	126	76.83	38	23.17	.511
	Yes	9	69.23	4	30.77	
5% glucose	No	112	77.78	32	22.22	.366
	Yes	23	69.70	10	30.30	
Dexamethasone	No	128	78.05	36	21.95	.083
	Yes	7	53.85	6	46.15	
Methadone	No	134	78.82	36	21.18	**.001**
	Yes	1	14.29	6	85.71	
Ondansetron	No	109	80.15	27	19.85	**.036**
	Yes	26	63.41	15	36.59	
Potassium chloride	No	133	76.00	42	24.00	1.000
	Yes	2	100.00	0	0.00	
Dipyrone	No	78	75.73	25	24.27	.860
	Yes	57	77.03	17	22.97	
Omeprazole	No	122	77.71	35	22.29	.263
	Yes	13	65.00	7	35.00	
Morphine	No	95	78.51	26	21.49	.344
	Yes	40	71.43	16	28.57	
Midazolam	No	132	78.11	37	21.89	**.019**
	Yes	3	37.50	5	62.50	
Ocreotide	No	131	77.51	38	22.49	.092
	Yes	4	50.00	4	50.00	
Furosemide	No	134	76.57	41	23.43	.419
	Yes	1	50.00	1	50.00	
Haloperidol lactate	No	124	75.61	40	24.39	.736
	Yes	11	84.62	2	15.38	
Cefepime	No	124	75.61	40	24.39	.736
	Yes	11	84.62	2	15.38	

*Fisher exact test. *P* values in bold are significant.

TABLE 4

Association of Numerical Variables With Adverse Effects Resulting From Hypodermoclysis (n = 177 Insertions): Univariate Analysis

Variable	Complications	N	Mean	SD	1st Q	2nd Q	3rd Q	*P* Value*
Body mass index	No	90	23.61	0.69	20.50	23.00	25.30	.074
	Yes	25	24.74	0.96	23.50	25.00	25.00	
Arm circumference	No	79	25.97	0.56	23.50	26.00	27.85	**.040**
	Yes	18	28.05	1.18	26.50	27.25	30.00	
Calf circumference	No	71	30.77	0.91	27.25	29.50	33.00	.062
	Yes	17	32.33	1.29	29.20	31.00	35.00	
Subcutaneous fold	No	135	18.44	1.16	10.00	15.00	24.00	**.020**
	Yes	42	22.86	2.01	12.00	22.50	32.00	
Length of stay	No	135	4.21	0.23	2.00	4.00	6.00	.074
	Yes	42	3.62	0.47	1.00	2.50	5.00	
Total medication dose	No	135	2.56	0.15	1.00	2.00	3.50	.117
	Yes	42	3.33	0.39	1.00	2.00	5.00	
Infusion volume	No	135	421.18	35.25	124.19	244.00	720.00	.087
	Yes	42	258.26	39.52	125.40	170.50	300.00	
Infusion rate	No	135	31.94	1.97	11.20	30.00	50.50	.895
	Yes	42	32.13	3.69	15.51	25.66	45.00	
Continuous infusion pump	No	135	1.15	0.08	1.00	1.00	1.00	.570
	Yes	42	1.43	0.23	0.00	1.00	2.00	
Bolus infusion	No	135	0.86	0.08	0.00	1.00	1.00	.931
	Yes	42	0.88	0.15	0.00	1.00	2.00	
Gravity infusion	No	135	0.60	0.07	0.00	0.00	1.00	**.006**
	Yes	42	1.02	0.15	0.00	1.00	2.00	

Abbreviations: Q, quartile; SD, standard deviation.
*Mann-Whitney. *P* values in bold are significant.

of medications. They concluded that ondansetron should be administered as a bolus and slowly, as it has an acidic pH of around 3.5.[36] Another systematic review that aimed to synthesize the current evidence for subcutaneous hydration and medication infusions to assess their methodological quality identified publications on ondansetron as having low evidence quality when they analyzed the evidence quality of studies on administration of drugs by subcutaneous infusion.[35]

TABLE 5

Final Logistic Model Related to Complications Resulting From Hypodermoclysis

Source	B	OR	95% CI	*P* value*
Intercept	−0.91	-	0.24–0.67	<**.001**
Sodium chloride = no	-	-	-	-
Sodium chloride = yes	−1.16	0.31	0.15–0.67	**.003**
Ondasetron = no	-	-	-	-
Ondasetron = yes	1.15	3.16	1.38–7.24	**.006**

Abbreviation: B, an unstandardized coefficient; CI, confidence interval; OR, odds ratio.
**P* values in bold are significant.

Even though the variables related to gravity infusion, skinfold, and BMI did not remain in the final logistic regression model, they are considered clinically important variables in the development of hypodermoclysis complications, which generates the need for further investigations to elucidate their contributions in the occurrence of adverse effects.

LIMITATIONS

The results presented in the present study must be analyzed based on some limitations. It was not possible to collect 100% of the anthropometric data from the research participants; they were collected for 79 participants (69%),

which may have influenced the magnitude of the association between BMI and the occurrence of adverse effects. Another limitation is the fact that adverse reactions were evaluated by a single person, and an assessment of the agreement level by the Kappa coefficient would be relevant in future studies to reinforce the data reliability. However, it is noteworthy that the researcher of this study has clinical experience and training as a specialist in providing care for older adults in palliative care. Data collection was only performed in a single palliative care unit in Brazil, making it impossible to generalize the results.

Lastly, the study brings important contributions to support the design of nursing actions focused on modifiable risk factors and consequently on improving the quality of care related to hypodermoclysis. It is evident that further studies should be conducted to elucidate the influence of risk factors for developing complications in older adults receiving hypodermoclysis.

CONCLUSION

The occurrence of adverse effects from hypodermoclysis in the investigated older adult population was low. 0.9% sodium chloride and ondansetron were independently associated with the occurrence of local adverse effects from hypodermoclysis. Sodium chloride (0.9%) has a protective effect (OR = 0.31 [95% CI, 0.15-0.67]), and ondansetron is associated with an adverse effect by hypodermoclysis (OR = 3.16 [95% CI, 1.38-7.24]).

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