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Midazolam for Post-Arrest Sedation in Pre-Hospital Emergency Care

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Original Article

Midazolam for Post-Arrest Sedation in Pre-Hospital Emergency Care

A Multicenter Propensity Score Analysis

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Summary

Background: An out-of-hospital cardiac arrest (OHCA) with return of spontaneous circulation (ROSC) may need to be treated with airway management, emergency ventilation, invasive interventions, and post-arrest sedation. We investigated the influence of the use of midazolam for post-arrest sedation on achieving post-resuscitation care targets and the associated risk of hemodynamic complications.

Methods: All emergency rescue missions of the Dresden, Gütersloh, and Lippe medical rescue services in the years 2019–2021 were reviewed to identify adult patients who had OHCA, unconsciousness, and sustained ROSC with spontaneous circulation until arrival at the hospital; the findings were supplemented with data from the German Resuscitation Registry. Patients who received midazolam (alone or in combination with other anesthetic agents) for post-arrest sedation were compared with those who did not. The endpoints were the regaining of a systolic blood pressure ≥ 100 mmHg, end-tidal pCO₂ 35–45 mmHg, and oxygen saturation (SpO₂) 94–98%. A propensity score analysis was used to adjust for age, sex, and variables potentially affecting hemodynamic status or the targets for oxygenation and ventilation.

Results: There were 2335 cases of OHCA among 391 305 emergency rescue missions. 571 patients had ROSC before arrival in the hospital (24.5%; female, 33.6%; age, 68 \pm 14 years). Of the 395

among them (69.2%) who were treated with post-arrest sedation, 249 (63.0%) received midazolam. Patients who received midazolam reached the guideline-recommended targets for oxygenation, ventilation, and blood pressure more frequently than those who were not sedated: the respective odds ratios and 95% confidence intervals were 2.00 [1.20; 3.34], 1.57 [0.99; 2.48], and 1.41 [0.89; 2.21].

Conclusion: The pre-hospital administration of midazolam leads to more frequent pre-hospital attainment of the oxygenation and ventilation targets in post-resuscitation care, without any evidence of an elevated risk of hemodynamic complications.

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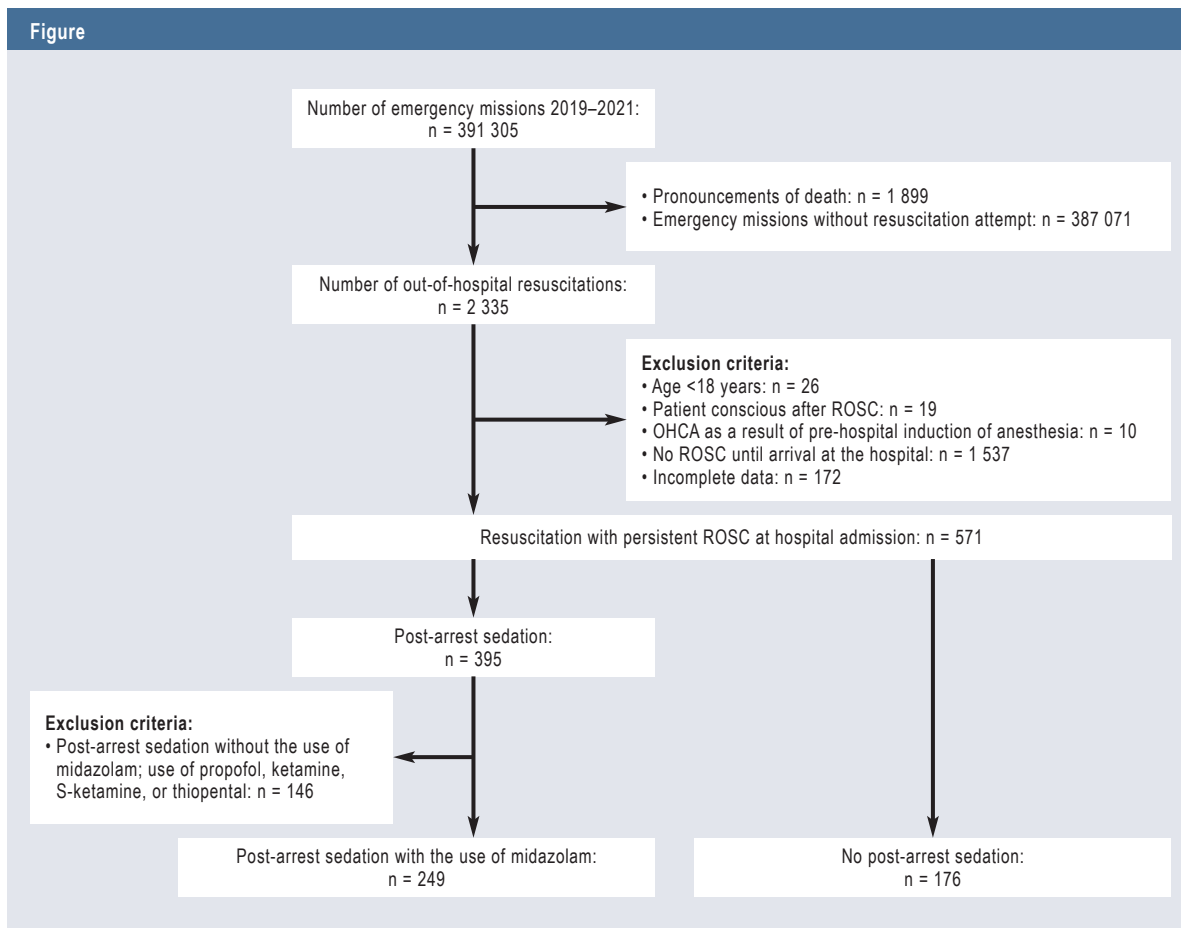
Survival rates following out-of-hospital cardiac arrest (OHCA) range from 8% to 18%. In 74% of cases, social participation of survivors is negatively impacted by OHCA-related morbidity. This highlights how relevant the management of OHCA is to society (1, 2). Apart from immediately initiating high-quality chest compressions and early defibrillation, early and targeted post-resuscitation care is becoming increasingly important for the prognosis of these patients and is thus recommended by the resuscitation guidelines (3, 4).

The guidelines recommend an ABC algorithm-based structured approach to pre-hospital and in-hospital emergency care, extended airway management with endotracheal intubation and its capnography monitoring, targeted ventilation treatment avoiding hyper- and hypoxemia (oxygen saturation (SpO₂) target: 94–98%),

hyper- and hypocapnia (end-tidal CO₂ (etCO₂) target: 35–45 mm Hg), and maintaining adequate perfusion pressure (systolic blood pressure ≥ 100 mm Hg/ mean arterial blood pressure ≥ 65 mm Hg) while avoiding periods of hypotension, as well as targeted temperature management (TTM, temperature target: 32–36 °C) (4).

During the critical phase immediately after the return of spontaneous circulation (ROSC), administration of post-arrest sedation is reasonable to facilitate extended airway management, optimum emergency respirator synchronization and performance of interventions such as coronary angiography and TTM (4–6). At the same time, there are risks

Figure



Flowchart of the applied inclusion and exclusion criteria
OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation

associated with the side effects of the substances administered (for example, acute hypotension, re-arrest) in this particularly vulnerable period immediately after ROSC. However, the guidelines on post-resuscitation care do not provide guidance on pre-hospital emergency anesthesia, as no evidence on the best method of post-arrest sedation in this specific patient population has yet become available (4, 7, 8). Our multicenter propensity score analysis investigates the influence of the use of midazolam for post-arrest sedation on achieving post-resuscitation care targets.

Material and methods

After the Westfalen-Lippe ethics committee had issued a positive opinion on the study on 3 October 2022 (ref. 2022–617-f-S), we performed a retrospective data analysis of the rescue service data of the State Capital of Dresden as well as the districts Gütersloh and Lippe with a population of approximately 1 275 000 inhabitants for the period 1 January 2019 to 31 December 2021; the findings were supplemented with data from the German Resuscitation Registry (9).

The following data were included in our analysis: data of patients aged ≥ 18 years who received pre-hospital resuscitation for OHCA of non-traumatic origin (defined as the need for chest compressions and/or defibrillation),

persistent decreased alertness after pre-hospital ROSC, presence of spontaneous circulation on admission to hospital, and administration of midazolam by the pre-hospital emergency rescue team for post-arrest sedation. Supplementary administration of other hypnotic agents was permitted if indicated by the attending emergency rescue team. The exclusion criteria were: no OHCA, no resuscitation attempt, patient aged < 18 years, traumatic circulatory arrest, no ROSC, patient conscious, OHCA as a result of pre-hospital emergency anesthesia, pronouncement of death, do-not-resuscitate order, no hospital admission, no spontaneous circulation on admission to hospital, and incomplete data with regard to the parameters to be included. An overview of the inclusion and exclusion criteria is provided in the *Figure*.

The following information was obtained: patient age and sex, suspected cause of circulatory arrest (cardiac, hypoxic, other), initial airway management (extraglottic airway, endotracheal intubation), switch from extraglottic airway to endotracheal tube intubation, airway complications (difficult airway management, defined as ≥ 1 intubation attempts or change of method for securing the airway; aspiration), and hemodynamic complications with need of administration of theodrenaline/cafedrine and/or of a vasopressor [norepinephrine or epinephrine],

administration of post-arrest sedation, substance and dose of the hypnotic, analgesic or muscle relaxant used, vital signs at hospital handover (SpO₂, etCO₂, systolic blood pressure), grouped according to the target corridors recommended in the guidelines on post-resuscitation care (SpO₂: 94–98% versus <94% or >98%; etCO₂: 35–45 mm Hg versus <35 mm Hg or >45 mm Hg, systolic blood pressure ≥100 mm Hg versus <100 mm Hg) (4).

The primary endpoint of our study was the influence of the administration of midazolam alone or in combination with an analgesic and/or muscle relaxant during post-arrest sedation on achieving the target parameters described above (4).

In order to perform the propensity score analysis, patients with midazolam administration were matched with patients without sedation, while adjusting for age, sex, and variables potentially affecting the targets for oxygenation and ventilation (circulatory arrest due to hypoxia), the initial airway device used (extraglottic airway, endotracheal intubation), the airway complications described, as well as for factors potentially affecting hemodynamic status (cardiac cause, hemodynamic complications).

Statistical analysis

Propensity score matching was performed because of the non-randomized allocation to the midazolam group or no-sedation group. The propensity score was estimated using logistic regression including all defined covariates, followed by 1 : 1 matching. We used a caliper width of 0.2 standard deviations of the logit-transformed propensity score to identify the best matching partners. The balance or risk factors was determined based on z-differences. Absolute z-differences of $\geq \sqrt{2}$ ($\geq 1,4142$) are considered abnormal (10). In addition, a kernel density estimate of the propensity score before and after the matching procedure was calculated (*eSupplements 1–5*). In order to measure the effect of midazolam administration, odds ratios (ORs) were calculated for the binary endpoints. After successful matching, stratified logistic regression models were used to analyze the primary endpoints, with the matching stratum included as a stratifying variable (10, 11). The estimated parameters were reported with the respective 95% Wald confidence intervals [95% CI]. All calculations were performed using the SAS statistical software package SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Over the study period, a total of 2335 cases of OHCA treated with resuscitation measures were observed in the participating study centers among 391 305 emergency rescue missions (0.59% of all emergency rescue missions; incidence in the years 2019–2021 approx. 183.1 per 100 000 population; [175.8; 190]). The *Figure* provides an overview of the evaluated emergency rescue missions after application of all inclusion and exclusion criteria.

571 patients (24.5%) of the 2335 cases of out-of-hospital resuscitation had sustained ROSC with spontaneous circulation before admission to hospital. Midazolam was used in 249 patients, i.e. in 63% of the 395 patients who were treated with post-arrest sedation (see *Figure*). The *eTable* provides an overview of the substances used and their combinations.

Table 1 shows the patient characteristics and in *Table 2* these are presented after propensity score matching, taking into account the administration of midazolam and midazolam in combination with an analgesic and/or muscle relaxant. The z-differences after matching indicate that a good balance was achieved. The results of the comparison of the propensity score-matched patient groups are shown in *Table 3*. The propensity score analysis showed that the guideline-recommended targets for oxygenation (OR: 2.00 [1.20; 3.34]) and ventilation (OR: 1.57 [0.99; 2,48]) were achieved significantly more frequently in the group of patients who received analgo-sedation with midazolam compared to the group without sedation, with no evidence of an increased risk of negative hemodynamic effects (OR: 1.41 [0.89; 2.21]) (*Table 3*). The *Supplements 6 and 7* show the propensity score matching and its results for the comparison of the post-arrest sedation groups with versus without the use of midazolam. Again, it was found that the administration of midazolam was associated with a clinically relevant advantage with regard to achieving the targets of oxygenation and ventilation.

Discussion

In our study, we performed a propensity score analysis to investigate the influence of the use of midazolam and/or analgesics or muscle relaxants for post-arrest sedation on achieving the hemodynamic and ventilatory post-resuscitation care targets. In 64% of the analgo-sedated patients, midazolam was used for post-arrest sedation. The guideline-recommended post-resuscitation care targets for oxygenation and ventilation were more frequently achieved by patients in whom midazolam was used for post-arrest sedation. This was associated with little evidence to support an increased risk of hemodynamic complications.

Administration of post-arrest sedation

One of the basic skills in emergency medicine is administering emergency anesthesia (7, 8). However, depending on the nature of the emergency and the patient's comorbidities, administering emergency anesthesia is often challenging and associated with relevant, possibly fatal complications (12–15). Although the guidelines on pre-hospital emergency anesthesia and airway management have contributed significantly to the standardization and improvement of patient care in specialist areas other than anesthesia too, they do not contain any recommendations as to how post-arrest sedation should be performed (7, 8). Only the guidelines of the European Resuscitation Council (ERC) recommend that those low-dose hypnotics, analgesics and rapid-onset muscle relaxants should be used with which the physician is most familiar (4, 7, 8, 12, 13). The available data suggest that post-arrest sedation is commonly administered after ROSC. As far as the authors are aware, however, its effects on post-resuscitation care targets have not yet been sufficiently evaluated. In addition to post-arrest sedation, intra-arrest sedation may also play a role in the future: Even though cognitive activity and awareness during cardiac arrest and the subsequent post-resuscitation period have so far been only inadequately studied, the

Table 1

Characteristics of patients before propensity score matching

Parameter	Use of midazolam in total (n = 249)	No sedation (n = 176)	z-difference
Age in years (M ± SD)	69.86 ± 14.22	67.60 ± 14.02	1.18
Male sex [n (%)]	165 (66.3)	112 (63.6)	-0.56
Cardiac cause [n (%)]	180 (72.3)	109 (61.9)	2.24
Hemodynamic complications [n (%)]	121 (48.6)	88 (50.0)	-0.29
Cause hypoxia (%)	42 (16.9)	37 (21.0)	-1.07
Initial EGA [n (%)]	98 (39.4)	86 (48.9)	-1.95
Initial ETI [n (%)]	212 (85.1)	157 (89.2)	-1.26
Airway complications [n (%)]	43 (17.3)	27 (15.3)	0.53
	Midazolam alone (n = 81)	No sedation (n = 176)	
Age in years (M ± SD)	68.47 ± 15.05	67.40 ± 14.17	0.54
Male sex [n (%)]	52 (64.2)	112 (63.6)	-0.09
Cardiac cause [n (%)]	59 (72.8)	109 (61.9)	1.77
Hemodynamic complications [n (%)]	38 (46.9)	88 (50.0)	-0.46
Cause hypoxia [n (%)]	13 (16.0)	37 (21.0)	-0.98
Initial EGA [n (%)]	41 (50.6)	86 (48.9)	0.26
Initial ETI [n (%)]	65 (80.2)	157 (89.2)	-1.83
Airway complications [n (%)]	14 (17.3)	27 (15.3)	0.39
	Midazolam + analgesic (n = 62)	No sedation (n = 176)	
Age in years (M ± SD)	69.79 ± 13.84	67.40 ± 14.17	1.16
Male sex [n (%)]	38 (61.3)	112 (63.6)	0.33
Cardiac cause [n (%)]	46 (74.2)	109 (61.9)	1.83
Hemodynamic complications [n (%)]	33 (53.2)	88 (50.0)	0.44
Cause hypoxia [n (%)]	10 (16.1)	37 (21.0)	-0.88
Initial EGA [n (%)]	24 (38.7)	86 (48.9)	-1.40
Initial ETI [n (%)]	49 (79.0)	157 (89.2)	-1.84
Airway complications [n (%)]	10 (16.1)	27 (15.3)	0.15
	Midazolam + relaxant (n = 36)	No sedation (n = 176)	
Age in years (M ± SD)	70.17 ± 12.27	67.40 ± 14.17	1.20
Male sex [n (%)]	24 (66.7)	112 (63.6)	-0.35
Cardiac cause [n (%)]	27 (75.0)	109 (61.9)	2.52
Hemodynamic complications [n (%)]	18 (50.0)	88 (50.0)	0.00
Cause hypoxia [n (%)]	5 (13.9)	37 (21.0)	-1.59
Initial EGA [n (%)]	10 (27.8)	86 (48.9)	-2.41
Initial ETI [n (%)]	33 (91.7)	157 (89.2)	0.48
Airway complications [n (%)]	8 (22.2)	27 (15.3)	0.92
	Midazolam + relaxant + analgesic (n = 70)	No sedation (n = 176)	
Age in years (M ± SD)	68.44 ± 13.55	67.40 ± 14.17	0.54
Male sex [n (%)]	51 (72.9)	112 (63.6)	-1.43
Cardiac cause [n (%)]	48 (68.6)	109 (61.9)	1.00
Hemodynamic complications [n (%)]	32 (45.7)	88 (50.0)	-0.61
Cause hypoxia [n (%)]	14 (20.0)	37 (21.0)	-0.18
Initial EGA [n (%)]	23 (32.9)	86 (48.9)	-2.34
Initial ETI [n (%)]	65 (92.9)	157 (89.2)	0.96
Airway complications [n (%)]	11 (15.7)	27 (15.3)	0.07

EGA, extraglottic airway device; ETI, endotracheal intubation; M, mean; n, number of patients; SD, standard deviation

phenomenon of resuscitation-induced alertness is being increasingly reported: In a study including 567 patients with in-hospital cardiac arrest, 39.3% reported memories or perceptions indicative of consciousness during cardiac arrest and the subsequent post-resuscitation period (cardiopulmonary resuscitation-induced consciousness: 7.1%; consciousness in the post-resuscitation period: 7.1%; dream-like experiences: 10,7%; transcendent recalled experience of death: 21.4%) (16, 17). Therefore, it is sensible to evaluate standardized analgo-sedation concepts in this highly vulnerable patient population in prospective, randomized trials with the aim of supplementing the existing guidelines based on such findings (7, 8).

Use of midazolam for post-arrest sedation

Frequently, hemodynamic side effects and complications are attributed to the pharmacodynamic effects of the hypnotics used (7, 10, 13–15). Thus, it is reasonable to use hypnotic agents with few hemodynamic side effects in patients at risk of cardiac events (5, 7, 10, 13–15). The guidelines explicitly recommend the use of midazolam for the induction and maintenance of anesthesia in high-risk cardiac patients which may be the reason why midazolam was found to be the hypnotic agent most commonly used for post-arrest sedation in our study, too (7).

Influence of the use of midazolam for post-arrest sedation on achieving post-resuscitation care targets for oxygenation and ventilation

Although optimum therapeutic strategies for peri-arrest ventilation have not yet been sufficiently evaluated, they constitute an important component of initial post-resuscitation care. By reducing reperfusion injury, targeted mechanical ventilation influences the prognosis of these patients. This requires that both hyper- and hypoxemia as well as hyper- and hypocapnia are avoided (4, 15, 18–21). The available data suggest that sedation with midazolam allows to achieve the recommended targets for oxygenation and ventilation already in the prehospital phase, possibly due to enhanced synchronization to the emergency respirator (4). Thus, integrated in a structured management concept, post-arrest sedation has the potential to contribute to improvements in the treatment of cardiac arrest patients, provided that negative hemodynamic effects can be avoided.

Influence of the use of midazolam for post-arrest sedation on achieving hemodynamic post-resuscitation care targets

Data on the hemodynamic side effects of midazolam during post-arrest sedation are still scarce (4, 5, 22). A study on 64 patients with resuscitation and ROSC, investigating the hemodynamic effects of a combination of midazolam, fentanyl and rocuronium for pre-hospital induction of anesthesia—which was frequently used in our study too—, found that 6% to 16% of patients experienced significant drops in blood pressure with acute hypotension (5). The combination of midazolam und fentanyl showed the most favorable effects on the maintenance of mean arterial pressure (MAP) compared to other anesthetic agents (e.g. etomidate, propofol, thiopental) in the induction of anesthesia in high-risk cardiac patients with severe left

ventricular dysfunction during cardiac anesthesia (5, 23, 24). In surgical emergency patients, no change in MAP after induction of anesthesia was observed after administration of midazolam in comparison to ketamine, thiopental or a combination of midazolam and ketamine (5, 25). In our study, we also found little evidence of an elevated risk of hemodynamic complications associated with the use of midazolam for post-arrest sedation. Thus, midazolam appears to be a hypnotic suitable for use in post-arrest sedation; consequently, existing guidelines should be supplemented accordingly (7, 8).

Disadvantages of the use of midazolam for post-arrest sedation

While midazolam offers significant advantages due to its rapid onset of action, relatively short duration of action and broad therapeutic range, some disadvantages must be taken into account (26): It often takes 3–5 minutes to achieve a sufficient depth of anesthesia, as required e.g. for airway management. Therefore, midazolam is primarily recommended to be used as an additive induction agent in combination with fentanyl, sufentanil and/or rocuronium (7, 8, 26). Being more difficult to control than other anesthetic agents, using midazolam for post-arrest sedation makes neurological assessment for further prognostication challenging. Consequently, midazolam could contribute to interventions, such as TTM, being performed, with the risk of associated adverse events, and complicate the subsequent stay in the intensive care unit (4, 25, 26).

Alternative post-arrest sedatives

Propofol is widely used for anesthetic induction and maintenance; in our study too, it was the second most commonly used narcotic after midazolam. It is characterized by rapid onset of action, good reflex suppression, reduction of cerebral metabolism, and neuroprotective effects, which could be particularly useful in post-resuscitation care (7, 8, 26). For propofol as a GABA-A agonist, NMDA receptor antagonist and modulator of calcium influx, animal models found a reduction in exotoxicity and reperfusion injury, resulting from decreased reperfusion hyperemia, with better neurological outcomes compared to no-sedation (26–30).

However, in the light of its significant hemodynamic side effects, some authors consider propofol to be contraindicated in certain types of shock and its use for post-arrest sedation is not unproblematic (7, 8, 26, 29, 30).

Ketamine also offers rapid onset of action, as well as good analgesic and sedative effects. Given its indirect sympathomimetic effects, it is particularly recommended for anesthesia induction in hemodynamically unstable patients, although it is still considered contraindicated in high-risk cardiac patients, despite at times passionate discussions (7, 8, 26, 30). Being an NMDA receptor antagonist, ketamine has potentially neuroprotective effects that could prove beneficial during post-arrest sedation; however, these too have been under-researched to date (31). Thus, the aim of future studies should be to evaluate the effects of the various sedatives used for post-arrest sedation on the neurological treatment outcome as part of a bundle strategy.

Table 2

Characteristics of patients after propensity score matching*

Parameter	Use of midazolam in total (n = 162)	No sedation (n = 162)	z-difference
Age in years (M ± SD)	69.96 ± 14.24	67.59 ± 13.98	1.44
Male sex [n (%)]	98 (60.5)	103 (63.6)	0.57
Cardiac cause [n (%)]	109 (67.3)	109 (67.3)	0.00
Hemodynamic complications [n (%)]	114 (70.4)	80 (49.4)	3.96
Cause hypoxia [n (%)]	30 (18.5)	32 (19.8)	-0.28
Initial EGA [n (%)]	77 (47.5)	73 (45.1)	0.45
Initial ETI [n (%)]	148 (91.4)	144 (88.9)	0.75
Airway complications [n (%)]	36 (22.2)	27 (16.7)	1.27
	Midazolam alone (n = 78)	No sedation (n = 78)	
Age in years (M ± SD)	68.95 ± 15.10	67.87 ± 14.43	0.46
Male sex [n (%)]	51 (65.4)	51 (65.4)	0.00
Cardiac cause [n (%)]	56 (71.8)	56 (71.8)	0.00
Hemodynamic complications [n (%)]	37 (47.4)	35 (44.9)	0.32
Cause hypoxia [n (%)]	13 (16.7)	14 (17.9)	-0.21
Initial EGA [n (%)]	39 (50.0)	34 (43.6)	0.80
Initial ETI [n (%)]	65 (83.3)	65 (83.3)	0.00
Airway complications [n (%)]	14 (17.9)	15 (19.2)	-0.21
	Midazolam + analgesic (n = 61)	No sedation (n = 61)	
Age in years (M ± SD)	69.84 ± 13.95	69.39 ± 14.39	0.17
Male sex [n (%)]	38 (62.3)	39 (63.9)	0.04
Cardiac cause [n (%)]	45 (73.8)	45 (73.8)	0.00
Hemodynamic complications [n (%)]	32 (52.5)	32 (52.5)	0.00
Cause hypoxia [n (%)]	10 (16.4)	10 (16.4)	0.00
Initial EGA [n (%)]	24 (39.3)	22 (36.1)	0.37
Initial ETI [n (%)]	49 (80.3)	49 (80.3)	0.00
Airway complications [n (%)]	10 (16.4)	7 (11.5)	0.80
	Midazolam + relaxant (n = 34)	No sedation (n = 34)	
Age in years (M ± SD)	69.38 ± 12.03	68.15 ± 12.97	0.41
Male sex [n (%)]	22 (64.7)	21 (61.8)	-0.25
Cardiac cause [n (%)]	25 (73.5)	26 (76.5)	-0.28
Hemodynamic complications [n (%)]	16 (47.1)	18 (52.9)	-0.49
Cause hypoxia [n (%)]	5 (14.7)	4 (11.8)	0.36
Initial EGA [n (%)]	10 (29.4)	9 (26.5)	0.27
Initial ETI [n (%)]	31 (91.2)	30 (88.2)	0.40
Airway complications [n (%)]	6 (17.6)	5 (14.7)	0.33
	Midazolam + relaxant + analgesic (n = 68)	No sedation (n = 68)	
Age in years (M ± SD)	68.35 ± 13.59	68.12 ± 12.43	0.11
Male sex [n (%)]	50 (73.5)	53 (77.9)	0.60
Cardiac cause [n (%)]	47 (69.1)	47 (69.1)	0.00
Hemodynamic complications [n (%)]	30 (44.1)	29 (42.6)	0.17
Cause hypoxia [n (%)]	14 (20.6)	10 (14.7)	0.91
Initial EGA [n (%)]	22 (32.4)	24 (35.3)	-0.36
Initial ETI [n (%)]	63 (92.6)	63 (92.6)	0.00
Airway complications [n (%)]	10 (14.7)	12 (17.6)	-0.47

*The differences in the size of the subgroups are defined by the various substance combinations and corresponding matching partners from the group of patients without post-arrest sedation.

EG, extraglottic airway device; ETI, endotracheal intubation; M, mean; SD, standard deviation

Table 3

Results of the propensity score analysis*

Outcome of treatment	Use of midazolam in total (n = 162)	No sedation (n = 162)	Odds ratio [95% CI]
SpO ₂ 94–98 % [n (%)]	61 (37.6.0)	39 (24.1)	2.00 [1.20; 3.34]
etCO ₂ 35–45 mm Hg [n (%)]	57 (35.2)	40 (24.7)	1.57 [0.99; 2.48]
Systolic blood pressure > 100 mm Hg [n (%)]	105 (64.8)	92 (56.8)	1.41 [0.89; 2.21]
	Midazolam alone (n = 78)	No sedation (n = 78)	
SpO ₂ 94–98 % [n (%)]	27 (34.6)	17 (21.8)	2.43 [1.01; 5.86]
etCO ₂ 35–45 mm Hg [n (%)]	31 (39.7)	19 (24.3)	1.92 [0.98; 3.76]
Systolic blood pressure > 100 mm Hg [n (%)]	57 (73.1)	47 (60.3)	1.67 [0.88; 3.16]
	Midazolam + analgesic (n = 61)	No sedation (n = 61)	
SpO ₂ 94–98 % [n (%)]	23 (37.7)	12 (19.7)	2.38 [1.04; 5.43]
etCO ₂ 35–45 mm Hg [n (%)]	21 (34.4)	18 (29.5)	1.30 [0.57; 2.97]
Systolic blood pressure > 100 mm Hg [n (%)]	36 (59.0)	36 (59.0)	1.00 [0.45; 2.23]
	Midazolam + relaxant (n = 34)	No sedation (n = 34)	
SpO ₂ 94–98 % [n (%)]	11 (32.4)	3 (8.8)	5.00 [1.10; 22.82]
etCO ₂ 35–45 mm Hg [n (%)]	10 (29.4)	5 (14.7)	2.25 [0.69; 7.31]
Systolic blood pressure > 100 mm Hg [n (%)]	26 (76.5)	15 (44.1)	2.83 [1.12; 7.19]
	Midazolam +relaxant + analgesic (n = 68)	No sedation (n = 68)	
SpO ₂ 94–98 % [n (%)]	26 (38.2)	15 (22.1)	2.00 [0.97; 4.12]
etCO ₂ 35–45 mm Hg [n (%)]	27 (39.7)	16 (23.5)	1.92 [0.95; 3.85]
Systolic blood pressure > 100 mm Hg [n (%)]	44 (64.7)	43 (63.2)	1.06 [0.54; 2.10]

*The differences in the size of the subgroups are defined by the various substance combinations and corresponding matching partners from the group of patients without post-arrest sedation.
etCO₂, end-tidal CO₂; BPsys, systolic blood pressure; SpO₂, oxygen saturation measured by pulse oximetry

Limitations

The limitations of our study arise from the general disadvantages of retrospective studies. There is a potential risk of selection bias, because patients who were sedated with midazolam may have died in the pre-hospital setting as a result of the administration of midazolam—although midazolam is explicitly recommended in the guidelines for hemodynamically unstable patients—and thus would have been excluded from the study population (5, 7). In a propensity score analysis, it is not possible to consider all confounders, as some may not have been documented (for example, the emergency physician’s experience or specialty [confounding by indication]). Future research projects could evaluate the influence of post-arrest sedation in patients who died in the pre-hospital setting, using, for example, a nested case-control study design, or address potentially unmeasured confounders by performing an instrumental variable analysis. Post-arrest sedation using midazolam alone or in combination with other substances was not standardized, but left to the discretion of the emergency physicians. For this reason, future studies should evaluate structured post-arrest sedation protocols. The pre-hospital ventilation regime was not covered, which could have influenced the oxygenation and ventilation results. However, it can be assumed that the set pre-hospital ventilation regimes were intended to achieve the target corridors for oxygenation and ventilation. The optimum peri-arrest ventilation strategies, which integrate

post-arrest sedation, should be investigated in further studies. Technical limitations of pre-hospital monitoring systems, affecting measurements in patients with severe shock or hypothermia, may have resulted in incorrect measurements, so that the proportion of patients achieving the respective target parameters may have been underestimated. Since the post-resuscitation care targets refer to the time of hospital handover, they do not allow any statement to be made about the type, duration and extent of any potential pre-hospital deviations from these targets or how quickly these targets were achieved. While it is known that deviations from the recommended target parameters have an impact on the prognosis of these patients, the present study does not allow any conclusions to be drawn about the neurological outcome of the treatment.

Conclusions

The use of midazolam for post-arrest sedation leads to more frequent pre-hospital attainment of the oxygenation and ventilation targets in post-resuscitation care, without any evidence of an elevated risk of hemodynamic complications. Future guidelines should be complemented by recommendations on post-arrest sedation and future studies should also evaluate the role of midazolam and other post-arrest sedation regimes with regard to neuroprotective effects.

REFERENCES - Available on request

QUESTIONNAIRE

E7(25)

Midazolam for Post-Arrest Sedation in Pre-Hospital Emergency Care

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark all the correct answers.

Introduction

Question 1: What is the range of survival rates following out-of-hospital cardiac arrest (OHCA)?

- A: 8% to 18%
- B: 20% to 30%
- C: 40% to 50%
- D: 60% to 70%

Question 2: In what percentage of cases is social participation of OHCA survivors negatively impacted by OHCA-related morbidity?

- A: 24%
- B: 44%
- C: 64%
- D: 74%

Question 3: What are the recommended oxygen saturation (SpO₂) and end-tidal CO₂ (etCO₂) targets according to resuscitation guidelines? (More than one answer may be correct)

- A: SpO₂ target: 94–98%
- B: SpO₂ target: 90–95%
- C: etCO₂ target: 35–45 mm Hg
- D: etCO₂ target: 30–40 mm Hg

Question 4: What is the primary purpose of this multicenter propensity score analysis study?

- A: To evaluate survival rates after OHCA
- B: To investigate the influence of midazolam use for post-arrest sedation on achieving post-resuscitation care targets
- C: Comparing different defibrillation techniques
- D: To assess the effectiveness of chest compressions

Materials and Methods

Question 5: Which of the following were inclusion criteria for the study? Patients aged ≥ 18 years.....? (More than one answer may be correct)

- A: Who received pre-hospital resuscitation for OHCA of non-traumatic origin
- B: With persistent decreased alertness after pre-hospital return of spontaneous circulation (ROSC)
- C: With the presence of spontaneous circulation on admission to hospital
- D: Irrespective of the administration of midazolam for post arrest sedation by the pre-hospital rescue team

Question 6: TRUE or FALSE?

"The primary endpoint of the study was to determine whether administering midazolam (either alone or combined with analgesics and/or muscle relaxants) during post-arrest sedation helps achieve specific target parameters."

- A: TRUE
- B: FALSE

Results

Question 7: What were the key findings regarding midazolam administration in post-arrest sedation according to the propensity score analysis?

- A: Midazolam significantly increased the risk of negative hemodynamic effects
- B: Midazolam was associated with significantly better achievement of oxygenation targets and ventilation targets without evidence of increased hemodynamic risks
- C: Midazolam was used in only 24 (5%) of patients with sustained ROSC, limiting the statistical power of the analysis
- D: Midazolam showed no significant difference in achieving guideline-recommended targets compared to patients without sedation

Discussion

Question 8: What percentage of analgosedated patients received midazolam for post-arrest sedation?

- A: 24%
- B: 44%
- C: 64%
- D: 84%

Question 9: How does targeted mechanical ventilation influence the prognosis of cardiac arrest patients?

- A: By reducing reperfusion injury
- B: By increasing reperfusion injury
- C: It has no effect on prognosis
- D: The influence is unknown

Question 10: What are the potential advantages of midazolam for post-arrest sedation?

- A: Rapid onset of action
- B: Relatively long duration of action
- C: Broad therapeutic range
- D: Easy to control depth of anesthesia

Question 11: Which hypnotic agent is characterized by rapid onset of action, good reflex suppression, reduction of cerebral metabolism, and neuroprotective effects?

- A: Midazolam
- B: Propofol
- C: Ketamine
- D: Thiopental

Question 12: For which type of patient is ketamine particularly recommended for anaesthesia induction?

- A: Hemodynamically stable patients
- B: Hemodynamically unstable patients
- C: High-risk cardiac patients
- D: Paediatric patients

Question 13: What should the aim of future studies be regarding sedatives used for post-arrest sedation?

- A: To evaluate the effects on neurological treatment outcomes
- B: To assess the impact on survival rates
- C: To determine the most cost-effective sedative
- D: To investigate patient satisfaction with different sedatives

Limitations

Question 14: What is a limitation of this study due to its retrospective nature?

- A: Small sample size
- B: Lack of long-term follow-up
- C: Inadequate statistical analysis
- D: Selection bias

Conclusion

Question 15: What do the authors conclude about the use of midazolam for post-arrest sedation?

- A: It is associated with an elevated risk of hemodynamic complications
- B: It should be avoided in post-resuscitation care
- C: It leads to more frequent pre-hospital attainment of oxygenation and ventilation targets
- D: Its effects on neurological outcomes are well-established

THE END



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ANSWER SHEET

E7(25)

Midazolam for Post-Arrest Sedation in Pre-Hospital Emergency Care

	*Time spent on activity						hour					min
	A	B	C	D	E		A	B	C	D	E	
1						9						
2						10						
3						11						
4						12						
5						13						
6						14						
7						15						
8												

You can complete any one, or all the parts of this activity.

How relevant was the content of this activity to your scope of practice?			
			
Not at all	Somewhat	Mostly	Extremely

RETURN ANSWER SHEET TO

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