

## Research Article

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## Use of Remimazolam for Procedural Sedation in Acute Subdural Hematoma Evacuation

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### Introduction

Benzodiazepines (BDZs) (Figure 1 shows the structural formula) represent a group of drugs widely used in anesthesia to achieve hypnosis, anxiolysis and anterograde amnesia [1]. They are classified based on their pharmacokinetics as drugs with short, intermediate and long half-lives. The chemical structure of BDZs is composed of a benzene ring coupled to seven heterocyclic structures having two nitrogen atoms in positions 1 and 4 (FIGURE 1). These molecules bind to the  $\gamma$ -aminobutyric acid (GABA) type A receptor in the postsynaptic membranes, causing GABA channels to open and allowing the massive intake of chloride ions into the cell, thus inducing hyperpolarization of the cell membrane, which becomes unable to conduct nerve impulses [2].

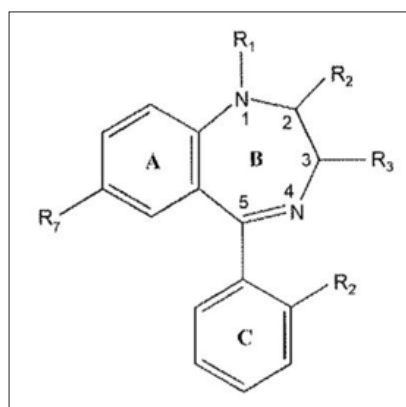


**Figure 1:** Structural Formula of Benzodiazepines

Remimazolam is a benzodiazepine synthesized in 1999 by Glaxo Smith Kline and later developed by PAION [3].

This molecule possesses a chemical structure similar to that of other benzodiazepines such as midazolam, but characterized by the addition of a carboxylic acid ester bond to the benzodiazepine ring (FIGURE 2). This modification makes its metabolism independent of organ function and completely dependent on plasma esterase-mediated hydrolysis, which, by breaking the ester bond, inactivates the molecule [4].

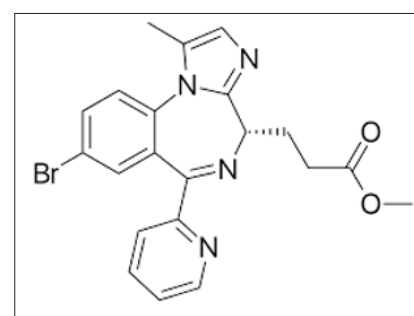


**Figure 2:** Structural formula of remimazolam

Remimazolam is a high-affinity ligand for the GABA-A receptor in the nervous system. Clinically, mirroring other BDZs, it exhibits dose-dependent sedative, anxiolytic, and amnesic effects. Based on its chemical properties, this latest-generation benzodiazepine is characterized by rapid onset and ultra-short duration. As with other molecules belonging to the same group, its effects can be antagonized by the administration of flumazenil [3]. Remimazolam's context-sensitive half-life profile allows for rapid elimination even after prolonged infusions [5], although this method of administration is still off-label in Italy.

Sedation is a procedure performed in anesthesiology that aims to reduce discomfort, pain, and anxiety in patients undergoing an invasive procedure [6]. Among the drugs used to achieve sedation are listed midazolam, propofol, and dexmedetomidine [7], however, each of the above-mentioned drugs has adverse effects: respiratory depression, hypotension, bradycardia, etc. [8-10]. An ideal sedative drug should have ultra-rapid-acting sedative and hypnotic activity, and should be easy to handle with minimal adverse effects [11].

Remimazolam has been successfully used to induce and maintain procedural sedation and general anesthesia, thanks to its rapid onset, short half-life, rapid recovery time, low accumulation after continuous infusion, and few adverse effects compared to those of other BDZs [12]. These characteristics make remimazolam a versatile and useful sedative drug for various types of procedures, even in elderly patients with comorbidities or at high anesthetic risk [13].

Remimazolam was approved in China for sedation during gastroscopy in December 2019 and for colonoscopy in June 2020; it was approved for procedural sedation in the United States in June 2020 and in the European Union and South Korea in August 2021. The same molecule was approved for use in general anesthesia in Japan in January 2020 and in China in November 2021. The compassionate use of remimazolam in Intensive Care Units was approved in Belgium in August 2020. [14-22].

### Materials and Methods

Regarding the use of remimazolam in neurosurgical procedures, there are few data in the literature [23-24]. Few datasets available are about stereotactic functional neurosurgery procedures where, given that general anesthesia prevents real-time neurological assessment, which is mandatory for optimizing therapeutic outcomes, we are in need of better options about the administration of sedative drugs in addition to local anesthesia [25]. Other studies have been conducted on the use of this ultra-short-acting benzodiazepine in awake craniotomy, where intraoperative neurological assessment is essential.

In our observational study, after authorization from our scientific ethics committee (Comitato Etico Campania Centro established pursuant to Resolution of the Campania Regional Council no. 16 of 01.23.2014), we enrolled 16 patients undergoing neurosurgical evacuation of acute subdural hematoma. All patients aged between 18-85 years were included.

Enrolled patients underwent neurological assessment performed using the Glasgow Coma Scale (GCS), had a score greater than 8.

Patients with either ASA risk classification system > 3, peripheral oxygen saturation on room air < 90% and/or BMI > 35 Kg/m<sup>2</sup> were excluded. Gender wise, of the 16 enrolled patients 12 were males and 4 were females.

In addition to remimazolam, to the patient was administered an opioid i.v. (fentanyl) for pain relief and local anesthesia (0.5% ropivacaine) was administered by a neurosurgeon.

In the operating room, all patients had the following vital signs monitored: peripheral oxygen saturation (SpO<sub>2</sub>), continuous electrocardiogram (ECG), and non-invasive blood pressure (NIBP).

Premedication was performed with atropine 0.5 mg, and a dose of remimazolam 0.075 mg/kg was administered, followed by an opioid drug (fentanyl 1 mcg/Kg) for pain relief and local anesthesia (0.5% ropivacaine) was administered by a neurosurgeon. Spontaneous breathing was maintained during the whole procedure with oxygen supplementation via nasal cannula with a flow rate of 3 L/min.

Primary target of the study was to maintain the stability of the aforementioned vital signs while ensuring at the same time an adequate deepness of sedation during the procedure (Ramsay 4). The collected data showed that the mean time needed to reach a Ramsay score 4 as target for the sedation was just above a minute

(76 seconds); eleven patients required supplemental administration of remimazolam 0.025 mg/kg, with a mean time from the first dose up to 9 minutes. Three patients did not require supplemental doses of remimazolam, despite the procedure lasting between 24 and 30 minutes.

None of the patients experienced episodes of oxygen desaturation with SpO<sub>2</sub> <95%, bradycardia with heart rate < 50 bpm, or hypotension with mean arterial pressure < 65 mmHg.

None of the patients required flumazenil to reverse the effect of remimazolam. At the end of the procedure, all patients had an neurological status with an Aldrete score of 10.

### Discussion

The anesthetic goal during subdural hematoma evacuation surgery is to maintain cerebral perfusion while preventing secondary brain injury through careful management of intracranial pressure, blood pressure, and oxygenation. The procedure can be performed under either general anesthesia (GA) or local anesthesia with sedation (LA); studies in literature show that the LA technique is superior to the GA technique in terms of less complications, less duration of surgery and hospital stay, but no differences have been found in terms of mortality and need for reintervention [26]. In theory, reducing the overall duration of subdural hematoma evacuation surgery, performed under local anesthesia with sedation, could reduce the likelihood of surgical complications, thus leading to less postoperative intensive care and a shorter hospital stay. Furthermore, a shorter surgical procedure is associated with a reduced risk of thromboembolism and hypothermia. Among the most common complications of general anesthesia are postoperative pulmonary atelectasis, hemodynamic instability, and aspiration resulting in pneumonia.

The most commonly used sedatives for subdural hematoma evacuation are propofol and dexmedetomidine. However, the use of propofol is often associated with significant hemodynamic instability and poor patient cooperation, resulting in episodes of respiratory depression followed by hypoxia and lower MAP resulting in lower cerebral blood flow. Although dexmedetomidine provides better sedation (in terms of less adverse effects) and a better recovery time than propofol, its clinical use is limited due to prolonged recovery times and the risk of bradycardia.

Remimazolam, an ultra-short-acting GABA receptor agonist, with its rapid onset and rapid clearance allows for rapid reversal of the sedative effect with the administration of flumazenil and exhibits significant anterograde amnesia, similar to other benzodiazepines with longer half-lives. These characteristics position remimazolam as an ideal sedative agent for short procedures.

### Conclusions

Our study shows that remimazolam is an excellent sedative for the evacuation of subdural hematomas, always combined with local anesthesia and administration of an opioid agent, as it has a safety profile that maintains stable vital signs and no incidence of respiratory depression. Further studies are needed to confirm the results of this study.

**Table 1**

| Age | Gender | BMI | ASA | Onset sec. | Offset min. | Time of procedure min. | Rescue doses | Hemodynamic stability | Desaturation (SpO2 < 5%) | Flumazenil need |
|-----|--------|-----|-----|------------|-------------|------------------------|--------------|-----------------------|--------------------------|-----------------|
| 79  | M      | 27  | 3   | 45         | 10          | 25                     | 1            | yes                   | no                       | no              |
| 85  | M      | 27  | 3   | 45         | 8           | 30                     | 2            | yes                   | no                       | no              |
| 75  | F      | 25  | 3   | 48         | 10          | 25                     | 1            | yes                   | no                       | no              |
| 82  | M      | 28  | 3   | 40         | 8           | 25                     | 2            | yes                   | no                       | no              |
| 79  | M      | 27  | 3   | 44         | 7           | 20                     | 2            | yes                   | no                       | no              |
| 80  | F      | 26  | 3   | 40         | 8           | 25                     | 2            | yes                   | no                       | no              |
| 84  | M      | 29  | 3   | 48         | 12          | 50                     | 3            | yes                   | no                       | no              |
| 79  | M      | 30  | 3   | 50         | 9           | 30                     | 3            | yes                   | no                       | no              |
| 78  | M      | 28  | 3   | 48         | 9           | 30                     | 3            | yes                   | no                       | no              |
| 73  | M      | 27  | 3   | 45         | 9           | 35                     | 3            | yes                   | no                       | no              |
| 78  | M      | 26  | 3   | 42         | 9           | 24                     | 3            | yes                   | no                       | no              |
| 75  | M      | 23  | 2   | 40         | 7           | 45                     | 5            | yes                   | no                       | no              |
| 77  | F      | 24  | 3   | 43         | 8           | 34                     | 3            | yes                   | no                       | no              |
| 75  | F      | 27  | 3   | 47         | 9           | 38                     | 4            | yes                   | no                       | no              |
| 79  | M      | 25  | 2   | 44         | 7           | 42                     | 5            | yes                   | no                       | no              |
| 70  | M      | 23  | 3   | 60         | 20          | 30                     | 0            | yes                   | no                       | no              |

**Table 2**

| Dati                                 | Mean values |
|--------------------------------------|-------------|
| Gender                               | 78          |
| BMI Kg/m <sup>2</sup>                | 26.4        |
| Onset Time (seconds)                 | 45          |
| Offset Time (minutes)                | 9.4         |
| Mean duration of procedure (minutes) | 32          |
| Rescue doses                         | 2.6         |
| Desaturation events                  | none        |
| Bradycardia                          | none        |
| Hypotension                          | none        |

## Notes

All authors have read and approved the final version of the manuscript

**Authors' Contribution:** Each author of this manuscript participated in data collection and writing of the work.

All authors read and approved the final version of the manuscript.

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**Ethical Approval for Research Involving Human Participants:** All procedures performed in this study involving human participants received ethical approval from the competent authorities (Comitato

Etico “Campania Centro”), as described in the appropriate section of the manuscript, and have been conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

**Informed Consent:** Informed consent was obtained from all participants prior to their inclusion in the study, as described in the appropriate section of the manuscript.

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