Successful transcranial motor evoked potentials monitoring under remimazolam-based anaesthesia: Case reports of two patients

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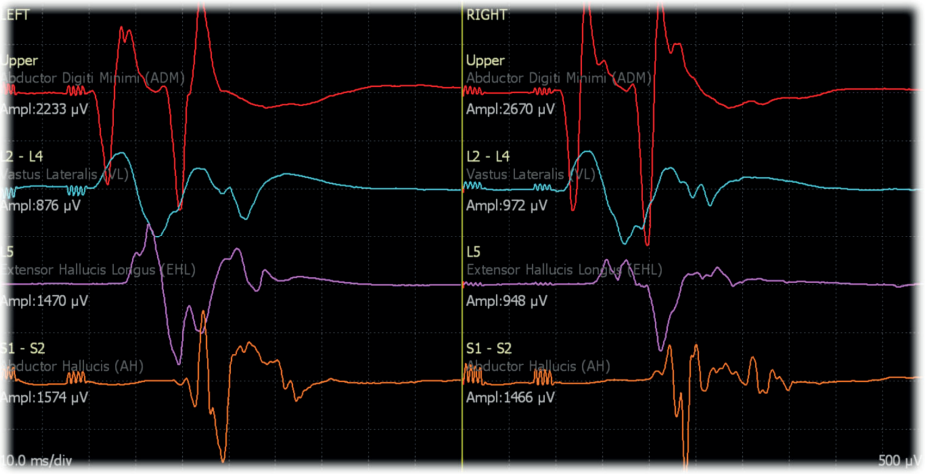
Introduction. Intraoperative neurophysiological monitoring is a standard in surgeries with an increased risk of iatrogenic neurological injury development. The gold standard for this monitoring modality is propofol-based total intravenous anaesthesia (TIVA). Although there seems to be no clinically significant complication for propofol administration in patients with soy, egg, or peanut allergies, a whole range of recommendations still prohibit propofol administration in patients with these allergies. Remimazolam is a new, ultra-short-acting benzodiazepine that can potentially be an alternative in cases of propofol contraindications in need of TIVA.

Case reports. We report two cases of a 19-year-old girl and a 17-year-old boy undergoing scoliosis surgery with transcranial motor evoked potentials monitoring (TcMEP). We chose remimazolam-based total intravenous anaesthesia due to the severe peanut and soy allergy, respectively. Total intravenous anaesthesia was maintained with remimazolam at a dose of 1.5-2 mg/kg/h and remifentanil at a dose of 0.5-0.8 μg/kg/min. Depth of anaesthesia was controlled using frontal EEG monitoring. TcMEP remained stable and showed no significant alterations throughout the surgeries. No new neurological deficits were detected after the surgeries.

Conclusion. Our results show that remimazolam-based anaesthesia may be a safe alternative to propofol-based anaesthesia for surgeries with an intraoperative neurophysiological monitoring, or patients with propofol contraindications but more data are needed.

TRANSCRANIAL MOTOR EVOKED POTENTIALS UNDER REMIMAZOLAM-BASED ANAESTHESIA



Remimazolam is a new ultra-short-acting benzodiazepine, recently approved for sedation in Europe.

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INTRODUCTION

Spinal fusion is one of the surgeries with a higher risk of the development of a new neurological deficit. The Scoliosis Research Society strongly recommends the use of intraoperative neurophysiological monitoring (IONM) to detect these potentially reversible complications[1,2]. Some anaesthetic agents and pathophysiological conditions can adversely affect IONM. Therefore, inhalation agents are not suitable, and the best option is total intravenous anaesthesia (TIVA), which combines propofol and opioids[3,4]. However, propofol can be contraindicated or not recommended in some cases. Although no link was found between propofol allergy and soy, egg, or peanut allergy in adults, anaesthesiologists should follow guidelines/recommendations[5-7]. Further, the safety of propofol administration in youths and children with the foodstuff allergies remains unclear[8]. Similarly, propofol is not a suitable drug for patients with a higher risk of propofol infusion syndrome, such as those on ketogenic diet therapy[9].

Remimazolam is a new, ultra-short-acting benzodiazepine, which was first approved for general anaesthesia in Japan in 2020. It is currently approved for procedural sedation and/or general anaesthesia in adults in multiple countries[10-12]. We report two cases of youths with peanut and soy allergies, who underwent scoliosis surgery under remimazolam-based TIVA. We successfully recorded transcranial motor evoked potentials (TcMEP) during surgery using remimazolam-based TIVA rather than propofol.

CASE REPORT 1

A 19-year-old girl (48 kg, 150 cm; ASA physical status II) with severe idiopathic scoliosis and a Cobb angle of 115° was scheduled for three-dimensional surgical correction with instrumented spinal fusion from T3 to L4 (see Fig. 1 – X-rays before and after surgery, Cobb angle 115°). Past medical history included bronchial asthma and peanut allergy with a clinical presentation of airway oedema. Preoperative neurological examination stated impaired dorsal flexion of the right foot thumb.

The patient was admitted to the orthopaedic department, and Halo-Gravity Traction was applied under local anaesthesia due to the rigidity of the scoliotic curve. This traction method was used to gradually stretch contracted soft tissues, thereby facilitating spinal mobilisation during surgery. By slowly lengthening the spinal column, the procedure also allowed the spinal cord to adapt gradually, reducing the risk of neurological injury during definitive corrective surgery.

The elective definitive surgery was postponed due to a respiratory tract infection and was performed 44 days after the Halo-gravity traction was placed. The spine fusion was performed under TIVA to allow the neurophysiologist-directed TcMEP monitoring. However, due to the anamnesis of severe peanut allergy, we decided to maintain the anaesthesia with the combination of remimazolam and remifentanil. TIVA was titrated using frontal EEG monitoring, as no Target Controlled Infusion (TCI) software for remimazolam has yet been developed, and a remifentanil infusion was administered following local TIVA protocol. The remimazolam dose was administered at a rate of 1.5–2 mg/kg/h, and the remifentanil dose at a rate of 0.5–0.7 μg/kg/min. A combination of remimazolam and remifentanil enables stable, sufficient neurophysiologist-directed TcMEP monitoring. TcMEP parameters remained unchanged during the entire surgery. The patient's vital functions (heart rate, blood pressure, SpO_2, $EtCO_2$, body temperature) remained stable and

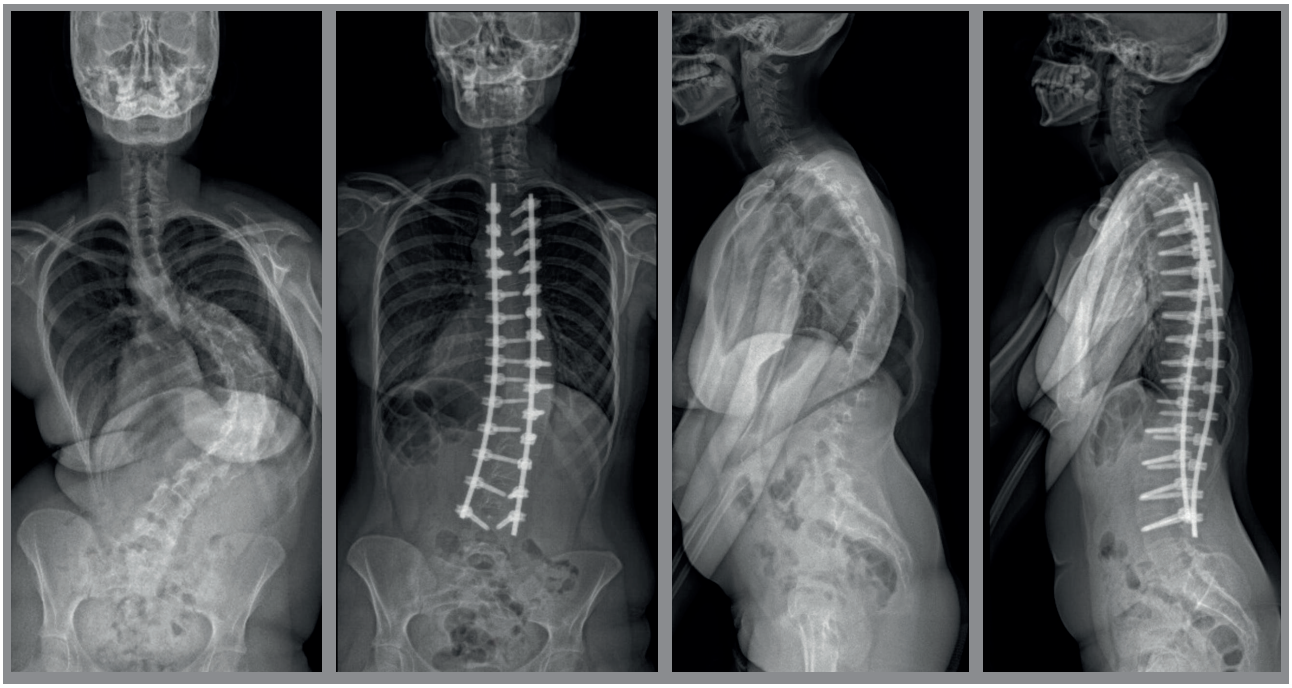

Fig. 1. X-rays before and after surgery, Cobb angle 115°.

within 25% of baseline values prior to surgery despite not receiving any medications to support them. Surgery was without complications, and the patient was extubated 9 minutes after the end of the operation, which lasted 6 hours and 20 minutes. The patient was then admitted to the orthopaedic intensive care unit (ICU).

The postoperative course was uneventful. We did not observe a new neurological deficit, including postoperative delirium, after the surgery. The patient began rehabilitation on the first postoperative day and was discharged 8 days later. The 5-month follow-up yielded a favourable outcome, with compensated scoliosis and no new neurological deficit.

CASE REPORT 2

A 17-year-old boy (weight 80 kg; height 182 cm, ASA physical status II) with idiopathic scoliosis and a Cobb angle of 74°, scheduled for three-dimensional surgical correction with instrumented spinal fusion T4 to L4 (see Fig. 2 – X-rays before and after surgery, Cobb angle 74°). Past medical history was seasonal bronchial asthma and anaphylactic reaction to soy. The preoperative neurological examination did not detect any neurological deficit.

The patient was admitted to the orthopaedic department for scoliosis correction. The surgery was under TIVA, allowing surgeon-directed TcMEP monitoring. Due to the patient's history of anaphylactic reaction to soy, we decided to maintain the TIVA as the combination of remimazolam and remifentanil. We used frontal EEG monitoring again to titrate the depth of anaesthesia. The remimazolam dose was administered at a rate of 1.5–1.8 mg/kg/h, and the remifentanil dose at a rate of 0.7–0.8 μg/kg/min following local protocol for TIVA. The surgeon-directed TcMEP monitoring remained stable throughout the entire surgery, with no change in TcMEP parameters (see Fig. 3 – Surgeon-directed transcranial motor evoked potentials under remimazolam-based total intravenous anaesthesia). The patient's vital functions remained within 20% of baseline despite not receiving any medication to support them. Surgery was uncomplicated, and the patient was extubated 5 minutes after the end of the 6-hour surgery. The patient was then admitted to the orthopaedic ICU.

The postoperative course was uneventful, and no new neurological deficit was reported after surgery. The patient began rehabilitation on the first postoperative day and was discharged 7 days later. The 1-month follow-up yielded a favourable outcome, with no new neurological deficit.

DISCUSSION

We present one of the first case series in which TcMEP were successfully recorded during remimazolam-based TIVA. To our knowledge, this is the first report of two cases of remimazolam administration in a European population, as previous publications have originated from Asian countries[13-15]. From this perspective, our publication could be unique.

Intraoperative neurophysiological monitoring is a standard modality in spinal fusion surgeries for deformities, as recommended by the Scoliosis Research Society[2], to detect iatrogenic new neurological injury. The gold stan-

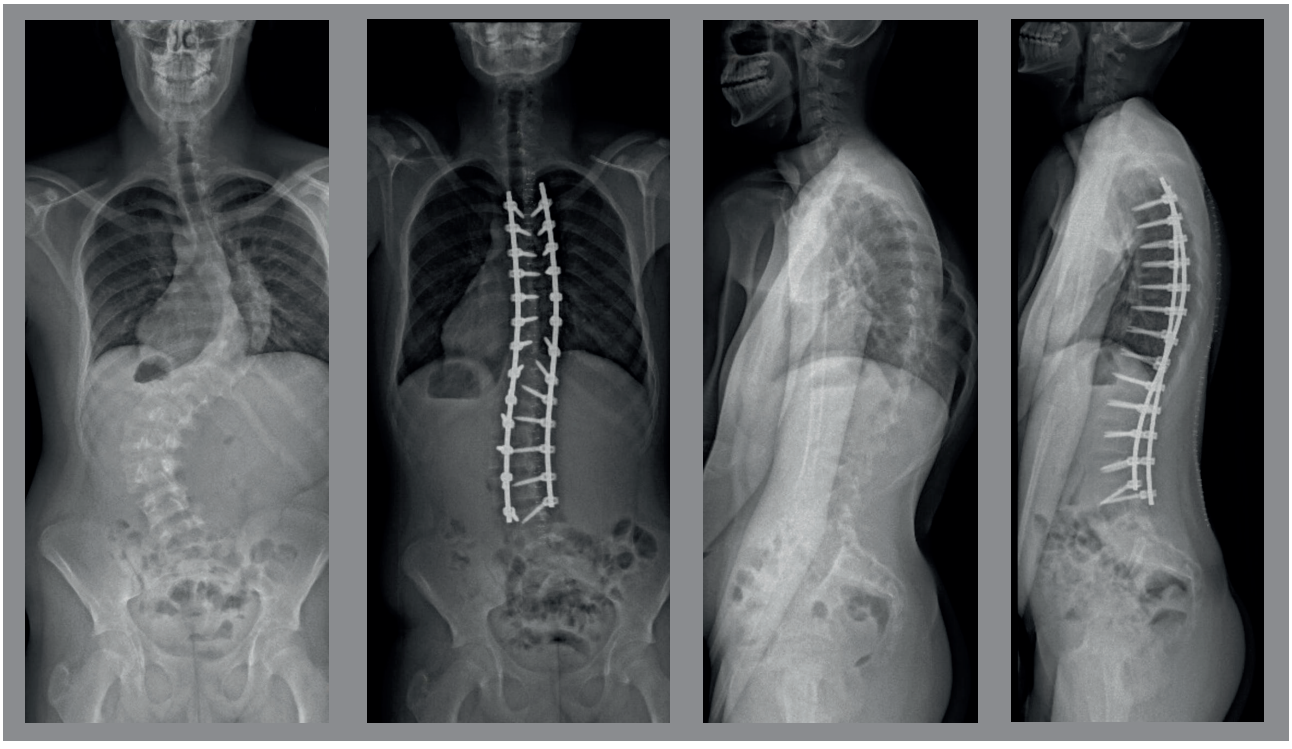

Fig. 2. X-rays before and after surgery, Cobb angle 74°.

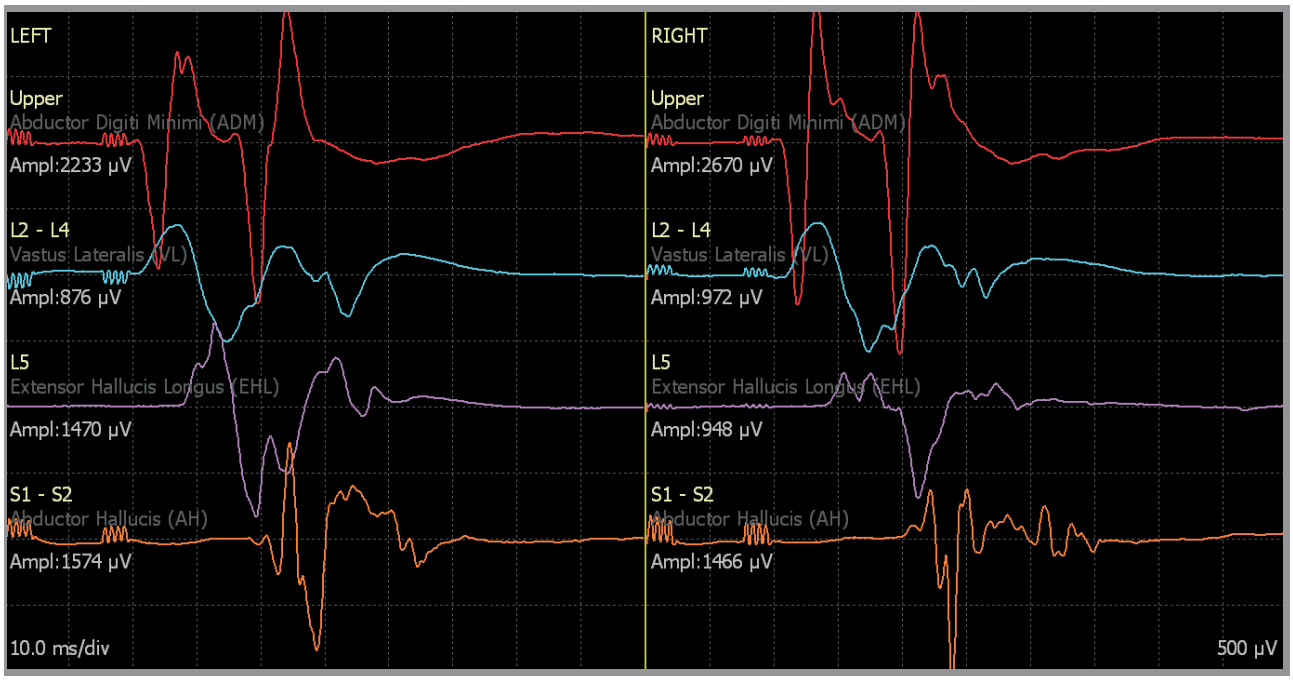

Fig. 3. Surgeon-directed transcranial motor evoked potentials under remimazolam-based total intravenous anaesthesia.

dard for anaesthetic management, which has little impact on TcMEP parameters, is a combination of opioids, specifically remifentanil, and propofol. However, propofol contraindications and the risk of propofol-related infusion syndrome, as well as propofol-dose-dependent TcMEP parameters alterations, remain a concern, necessitating an alternative drug. Another anaesthetic, such as thiopental, midazolam, or an inhalational anaesthetic, is not suitable for surgeries with TcMEP monitoring. Lately, publications from Asian countries have reported remimazolam as a promising and safe alternative to propofol for TIVA during surgeries with TcMEP monitoring[3,4].

Remimazolam is a new benzodiazepine with high affinity for gamma-aminobutyric acid type A ($GABA_A$) receptors to induce membrane hyperpolarisation. It combines the pharmacodynamics of benzodiazepines, such as midazolam, and pharmacokinetics like remifentanil[11,16]. Remimazolam's uniqueness lies in its chemical structure, which features an esterase linkage. Thanks to this, remimazolam is rapidly hydrolysed by plasma esterases regardless of liver or kidney functions. The first available publications describe a lower incidence of adverse events, such as hypotension, hypoxemia, or vomiting, comparing remimazolam to propofol. Furthermore, remimazolam has been successfully administered during surgeries with TcMEP monitoring as an alternative to propofol[13]. In addition, like other benzodiazepines, remimazolam has a specific antagonist, flumazenil. However, in light of its rapid metabolism, the need for flumazenil administration to reverse remimazolam's effect seems to be controversial due to the higher risk of its adverse effects, such as epileptic seizures or arrhythmias[16-18]. Compared to propofol, remimazolam appears to be a non-inferior drug. Compared with propofol, remimazolam was associated with a lower risk of hypotension after anaesthesia induction, injection pain, nausea and vomiting. In addition, patients in the propofol-based TIVA had a higher frequency of haemodynamic adverse effects, such as hypotension or heart rate fluctuation. However, data are preliminary, and we need more studies to provide strong evidence about future administration and side effect frequency[16,19-22].

Remimazolam has already been approved for procedural sedation and/or general anaesthesia as a safe alternative to other sedatives in Asia[10,13]. Therefore, we choose to use remimazolam to maintain anaesthesia as an alternative to propofol for our patients. We administered remimazolam at the upper limit of the dosing schedules reported in Asian publications, because the pharmacokinetic profiles of anaesthetics may differ between these populations after all. The dose of remimazolam for maintenance of general anaesthesia for the Asian population is expressed between 1–2 mg/kg/h[10,13,17]. The remimazolam dosage was altered for anaesthesia maintenance according to the frontal EEG values, targeted range from 40 to 60. Our dosage was titrated between 1.5–2 mg/kg/h. There appears to be a need to administer remimazolam at the upper limit of the dosage schedule in the European population, although further research is needed. However, our patients had a comparable perioperative course with stable TcMEP, even when the higher doses were administered. This corroborates the findings of the few publications released to date. When comparing remifentanil administration during remimazolam-based TIVA with that in our local propofol-based TIVA protocol, the remifentanil dose did not differ. The remifentanil dosage was similar to that reported in other publications, whether administered via manually-controlled infusion or TCI (ref.[23,24]).

Our two case reports had some limitations. One weakness is the small number of patients included in this case series. Second, the impact of remimazolam on TcMEP

monitoring, respectively, the effect of doses on TcMEP parameter alterations, remains unclear[25]. Further studies are needed to explore these limitations.

CONCLUSION

Based on our case reports, we are optimistic that remimazolam could serve as an alternative sedative to propofol in surgeries with TcMEP monitoring. Remimazolam can be administered to patients with contraindications to propofol and a risk of propofol-related infusion syndrome and represents a promising new agent for sedation and general anaesthesia. The upper limit of the remimazolam dosage schedule for maintaining anaesthesia appears adequate in the European population.

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Ethics approval: Ethical approval was not required as the case series was retrospective. Written informed consent was obtained from the patients or legal representatives to be used in this publication.

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