EJA

*Eur J Anaesthesiol* 2025; **42:**1–3

SHORT SCIENTIFIC REPORT

# Hypnotic and antinociceptive contribution of magnesium sulphate during balanced total intravenous anaesthesia in total thyroidectomy

*A randomised double-blind clinical trial*

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**Received** 8 January 2025 **Accepted** 6 May 2025



Editor,

Magnesium represents the fourth extracellular cation. Its sulphate heptahydrate salt (MS) has a therapeutic role as a calcium channel blocker. As a sympatholytic agent, it has been widely studied for reducing the systemic response to surgical stress, as well as its antinociceptive properties through a non-competitive antagonism on *N*-methyl-D-aspartate (NMDA) glutamate receptor.[1] More controversial is its contribution to the alteration of consciousness in the context of balanced general anaesthesia (GA).[2] Propofol and remifentanil exhibit pharmacodynamic synergy: propofol's $GABA_A$-mediated suppression of cortical and thalamic arousal complements remifentanil's μ-opioid inhibition of ascending nociceptive pathways, resulting in mutual potentiation enabling lower, nonaddictive opioid dosing and reducing hypnotic requirements, thereby minimising side effects and enhancing haemodynamic stability in balanced intravenous anaesthesia (TIVA). Several studies demonstrated an effect of MS as an enhancer of hypnotic agents. Nevertheless, the use of multimodal protocols with opioids have reduced sensitivity at determining the real effect of MS on the brain electrical activity and the depth of the hypnotic and antinociceptive component of GA.[3,4]

The purpose of this prospective, randomised, double-blinded clinical trial was to investigate the effect of MS on the hypnotic component of propofol TIVA, as assessed through the monitoring of the state entropy (SE) of the electroencephalogram and propofol consumption during total thyroidectomy (TT). In addition, the antinociceptive effect of MS was studied through the response entropy (RE), and haemodynamic variations such as heart rate (HR) and mean arterial pressure (MAP) during the induction of propofol-remifentanil GA and at the time of surgical incision. Approved by the Ethics Review Board (study number 2021/190) on 2 July 2021 and registered before patient enrolment under the EudraCT-number 2021-002824-19 on 27 July 2021, it followed Helsinki Declaration guidelines and Consolidated Standards of Reporting Trials (CONSORT) standards. Patients provided informed consent before participation.

Adult patients scheduled for elective TT were screened and randomised in a 1 : 1 ratio into two groups: Group MS (50 mg $kg^{-1}$ MS 10%) or Group CO (0.9% NaCl). The number of ml administered for both MS and placebo corresponded to half of the ideal body weight. The ideal body weight was computed in men as 50 + [0.91 × (height in centimetres – 152.4)] and in women as 45.5 + [0.91 × (height in centimetres – 152.4)]. Key exclusion criteria included patient refusal, ASA status IV, severe cardiac or renal insufficiency, obesity (BMI >35 kg $m^{-2}$), and neuromuscular disorders. Randomisation was computer-generated, with solutions prepared by uninvolved operating room nurses to ensure blinding of patients, surgeons, and anaesthesiologists collecting data.

All patients received preoperative etoricoxib 120 mg, followed by standard monitoring (ECG, pulse oximetry, blood pressure, and electroencephalogram (EEG) SE and RE. Anaesthesia was induced using target-controlled infusions (TCI) of propofol and remifentanil, with propofol titrated to achieve SE values between 50–60. Neuromuscular blockade was achieved with rocuronium. Intraoperative hypotension (MAP < 65 mmHg) was treated with ephedrine, and bradycardia (HR < 40 bpm) with atropine. Dexamethasone and ondansetron were administered to prevent postoperative nausea and vomiting. Postsurgery, patients received a multimodal analgesia regimen, including paracetamol, etoricoxib, and, if necessary, oxycodone for rescue pain relief.

Primary endpoints included propofol effect-site concentration to achieve SE 50–60 (Propofol Ce). Secondary endpoints encompassed SE, RE, heart rate (HR), and mean arterial pressure (MAP) evolution during induction and surgical incision. The anaesthesiologist recorded propofol and remifentanil doses, haemodynamic variations, and postoperative outcomes such as pain scores



DOI:10.1097/EJA.0000000000002216

(numerical rating scale (NRS) 0–10) and opioid consumption. Parameters were measured at predefined time points: 3 min before and during orotracheal intubation (OTI) and surgical incision, and at 1, 2.5, 5, 7.5 and 10 min thereafter.

The primary outcome was the between-group difference in Propofol Ce. Based on previous data from our institution (mean propofol Ce50–60 4.2 ± 0.39 μg ml$^{-1}$), sample size calculation determined 14 patients per group were required to detect a clinically significant 0.5 μg ml$^{-1}$ difference in Propofol Ce with 95% power and an alpha of 0.05. Considering a 25% dropout rate 36 patients were required. Statistical tests included Fisher's exact, χ2, Wilcoxon–Mann–Whitney and *t*-tests for demographic and non-repeated measures. Generalised linear mixed models (GLMM) were employed to assess time-group interactions in SE, RE, HR, and MAP over time.

Data were acquired between 21 October 2021 and 8 April 2022. Of 37 patients scheduled for elective TT, 1 declined participation, leaving 36 patients enrolled and randomised into two study groups (1 : 1 ratio). Three additional patients were excluded due to data loss on the primary outcome, resulting in an analysis of 33 patients. Patient characteristics were comparable between groups (Table 1).

At induction, propofol Ce [mean ± SD] was 4.03 ± −.77 μg ml$^{-1}$ in group CO and 3.79 ± 0.72 μg ml$^{-1}$ in group MS ($P = 0.39$). No significant differences were found between groups in anaesthesia induction duration, propofol dose to achieve RASS −5, total remifentanil or propofol dose, atropine/ephedrine use, postoperative pain, cumulative opioid consumption and Propofol Ce values at recovery (RASS −2; Table 1 ).

GLMM analysis showed no significant effect of group nor time-group interaction for Propofol Ce, Remifentanil Ce, SE, RE, HR or MAP during induction and after skin incision, except for an anecdotic time-group on MAP after skin incision ($P = 0.019$). Group MS showed a clinically irrelevant increase in MAP 7.5 min after incision [mean difference: 12.2 mmHg (95% CI: 24.2–0.2), $P = 0.048$, Cohen's $F = 0.37$] (Appendix 1, Supplemental Digital Content, http://links.lww.com/EJA/B149). Sensitivity analysis confirmed minimal effect sizes for SE, RE and hemodynamic parameters, supporting the robustness of the findings (Appendix 2, Supplemental Digital Content, http://links.lww.com/EJA/B150).

This study found no significant effect of preinduction MS on hypnotic depth or antinociceptive parameters during balanced GA for TT. MS did not reduce propofol requirements, enhance hypnotic depth (SE), or significantly influence nociceptive markers (RE, HR, MAP) or opioid consumption. Postoperative outcomes, including pain intensity and morphine use, were also unaffected, suggesting that MS does not provide substantial benefits in this surgical context.

The controlled setting, involving moderate nociceptive stimuli and standardised anaesthetic protocols, may have limited the observable impact of MS. Additionally, the dosing protocol, although consistent with prior studies, might not have been optimal for detecting subtle effects.

**Table 1** Demographic characteristics and postoperative evolution of secondary outcomes

| | Group CO n = 15 | Group MG n = 18 | *P-value* |
|---|---|---|---|
| Age (y) | 52.07 ± 9 | 47.67 ± 14.85 | |
| Sex | 3 (20) | 3 (16.7) | |
| ASA classification | | | |
| I | 7 (46.7) | 4 (23.5) | |
| II | 7 (46.7) | 13 (76.5) | |
| III | 1 (6.7) | 0 (0) | |
| Weight (kg) | 68.7 ± 14.2 | 69.1 ± 12.2 | |
| Height (m) | 1.67 (10.1) | 1.64 (9.9) | |
| History of alcohol chronic abuse | 6 (40) | 10 (55.6) | |
| Smoking patients | 3 (20) | 2 (11.1) | |
| Time to RASS -5 (min) | 5 [3.1 to 6.6] | 5.3 [3.3 to 7.8] | 0.98 |
| Time to $SE_{50-60}$ (min) | 8.7 ± 4.1 | 8.3 ± 3.2 | 0.76 |
| Propofol dose to $SE_{50-60}$ (mg kg$^{-1}$ min$^{-1}$) | 0.26 [0.25 to 0.3] | 0.25 [0.21 to 0.3] | 0.37 |
| Patients having received ephedrine | | | |
| At induction | 2 (13.3) | 1 (6) | 0.47 |
| After incision | 2 (13.3) | 0 (0) | 0.1 |
| Total intraoperative propofol dose (mg) | 1123 [943 to 1249] | 1194 [964 to 1364] | 0.55 |
| Total intraoperative remi dose (μg) | 740 [556 to 856] | 800 [665 to 1019] | 0.33 |
| Propofol Ce when RASS -2 (μg ml$^{-1}$) | 1.16 ± 0.31 | 1.28 ± 0.33 | 0.29 |
| Remi Ce when RASS -2 (ng ml$^{-1}$) | 0.67 ± 0.3 | 0.83 ± 0.4 | 0.21 |
| Total postoperative OME (mg) | 6 [0–12.75] | 6 [1.25–18.25] | 0.42 |
| Pain in PACU (NRS) | 2.1 [0–4.8] | 6.3 [1.1–8.2] | 0.06 |

Data are mean ± SD, median [IQR], and number (%). ASA, American Society of Anesthesiologists; Ce, effect site concentration; CO, control group; MG, magnesium group; OME, oral morphine equivalents; PACU, post-anaesthesia care unit; RASS, Richmond Agitation Sedation Scale; remi, remifentanil; SE, state entropy; Y, years. postoperative, after the first 24 postoperative hours

These findings challenge previous reports suggesting MS's anaesthetic-sparing properties, particularly in simplified anaesthetic regimens.[5–7]

While these results indicate that MS offers no clear advantage in this specific context, limitations such as the single-centre design, small sample size, and focus on TT may restrict generalisability. Although emerging nociception monitors (ANI, SPI, pupillometry) can offer complementary data, their requirement, training and limited evidence of their added predictive value over RE combined with haemodynamic variations led us to focus on SE–RE. A significant limitation of our study is the reliance on SE monitoring to assess hypnotic depth. This has been reported to have fundamental flaws in accurately detecting true depth of anaesthesia. This limitation of current depth of anaesthesia monitoring technology could partly explain the absence of an observed effect of magnesium sulphate on anaesthetic requirements and brain activity in our findings. Future research is encouraged to evaluate the role of MS in different surgical procedures, patient populations, and with alternative dosing regimens and monitoring. Further exploration of the potential interactions of MS with multimodal anaesthetic protocols and its effects on more invasive surgery could provide deeper insights into its anaesthetic and antinociceptive properties.

## Acknowledgements

Funding: This work was supported by the Department of Anaesthesia and Intensive Care Medicine, Liege University Hospital, Liege, Belgium. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Conflicts of interest

M.C. has received interview and speaker's honoraria from GE Healthcare, Aguettant and Baxter. M.C. is Associate Editor at the European Journal of Anaesthesiology. He is a member of the Belgian Association for Regional Anaesthesia Board and of the Scientific Committee of the European Society of Anaesthesiology and Intensive Care. V.B. has received funds and research support from Orion Pharma as well as honoraria from Medtronic, and Viatris. He is Deputy Editor-in-Chief of the Acta Anaesthesiologica Belgica, and has a consultancy contract with Edwards Medical. Other authors declare no conflicts of interest.

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