BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2025.05.055
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

Factors associated with a reduction in the preventive effect of intravenous dexamethasone on rebound pain after axillary brachial plexus block

Nassim Touil[1,*], Athanasia Pavlopoulou[1], Olivier Barbier[2], Xavier Libouton[2], Damien Gruson[3], Jean-Luc Gala[4] and Patricia Lavand'homme[1]

[1]Department of Anaesthesiology, Cliniques Universitaires St Luc, Catholic University of Louvain, Brussels, Belgium, [2]Department of Orthopaedic Surgery, Cliniques Universitaires St Luc, Catholic University of Louvain, Brussels, Belgium, [3]Department of Laboratory, Cliniques Universitaires St Luc, Catholic University of Louvain, Brussels, Belgium and [4]Centre for Applied Molecular Technologies, Catholic University of Louvain, Brussels, Belgium

*Corresponding author. E-mail: nassim.touil@saintluc.uclouvain.be

Abstract

Background: Rebound pain after regional anaesthesia remains a significant clinical problem. Intravenous dexamethasone is commonly used as an adjuvant to prevent rebound pain although its effectiveness varies among patients. We aimed to identify phenotypic and biological factors influencing glucocorticoid sensitivity contributing to dexamethasone resistance in the prevention of rebound pain.

Methods: Patients undergoing ambulatory upper limb surgery with an axillary brachial plexus block were enrolled prospectively to receive dexamethasone (0.1 mg kg^{-1} i.v.) before surgery. Preoperative factors analysed encompassed clinical aspects (central sensitivity, anxiety, and pain scores) and biological parameters (salivary cortisol, annexin-A1, and blood inflammatory markers). Postoperative outcomes comprised rebound pain incidence (numerical rating scale >7 within the first 24 h) and persistent pain at 3 months.

Results: Of the 104 patients included, 36 (34.6%) developed rebound pain. Preoperative nocturnal awakening pain (odds ratio [OR]=3.09, *P*=0.03), severe anxiety (OR=3.54, *P*=0.01), high catastrophising score (OR=4.14, *P*=0.01), and low salivary cortisol levels (<1147 pg ml^{-1}) (OR=3.33, *P*=0.02) were associated with an increased risk of rebound pain. Persistent pain at 3 months (27%) was associated with the presence of postoperative rebound pain (*P*=0.04).

Conclusions: Preoperative nocturnal pain, severe anxiety, high catastrophising, and low salivary cortisol levels are factors that might reduce the efficacy of dexamethasone in preventing rebound pain. These findings support the development of personalised preventive strategies.

Clinical trial registration: NCT05763433

Keywords: axillary brachial plexus block; dexamethasone; orthopaedic surgery; peripheral nerve block; rebound pain

Editor's key points

- Rebound pain after peripheral nerve blocks is a significant clinical problem that might have long-term sequelae. Intravenous dexamethasone is an effective adjuvant to prevent rebound pain.
- This study assessed individual variation in the effectiveness of dexamethasone in reducing rebound

Received: 5 January 2025; **Accepted:** 22 May 2025

pain after axillary brachial plexus block focusing on the phenotypic and biological factors that might contribute to dexamethasone resistance.
- Preoperative nocturnal pain, severe anxiety, high catastrophising, and low salivary cortisol levels were identified as factors that might reduce dexamethasone efficacy in preventing rebound pain and so contribute to variability in effect.
- Preoperative identification of these risk factors should support development of personalised preventive strategies.

Nearly 50% of patients undergoing surgery with regional anaesthesia, particularly under peripheral nerve block, develop rebound pain, characterised by a rapid and intense pain surge 12 to 24 h after the initiation of the peripheral nerve block, as its analgesic effects wear off.[1] As use of regional anaesthesia expands, particularly in ambulatory settings, rebound pain prevention has become a human and socio-economic priority. Rebound pain is associated with patient dissatisfaction, increased suffering, and unforeseen healthcare costs (emergency visits, unplanned consultations).[2,3] Risk factors for rebound pain have been identified which include female sex, younger age, bone surgery, and the lack of perioperative dexamethasone administration.[1] Dexamethasone, a long-acting glucocorticoid, is used in anaesthesia for its analgesic, antiemetic, and anti-inflammatory effects. It also prolongs the analgesic effect of peripheral nerve blocks, extends the time to the first analgesic request, and increases the block duration.[4,5]

Currently, i.v. dexamethasone administration appears to be the best preventive strategy against rebound pain after single-injection peripheral nerve block, with efficacy demonstrated in retrospective studies and randomised trials.[1,6–9] According to a recent systematic review, the number needed to treat (NNT) to prevent rebound pain with intraoperative administration of dexamethasone is 2.8.[8] The preventive effect of dexamethasone against the development of rebound pain when the peripheral nerve block wears off remains variable among patients,[10] with 23–42% of patients showing no preventive effect, indicating interindividual variability in effectiveness.[6,8]

In this context, aligning with the concept of personalised and stratified medicine, better understanding the individual factors influencing dexamethasone variability in effectiveness is important.[10] Various factors can affect sensitivity to endogenous glucocorticoids and, consequently, exogenously administered glucocorticoids.[11–13] Among these, chronic stress promotes glucocorticoid resistance in some individuals, altering responses to endogenous and exogenous cortisol.[11] Moreover, prolonged stress exposure in patients with chronic anxiety can disrupt the regulation of the hypothalamic–pituitary–adrenal axis, leading to hypocortisolism.[14–16] Chronic inflammatory conditions, such as rheumatoid arthritis, also reduce glucocorticoid sensitivity and limit their anti-inflammatory effects.[17,18] Annexin-A1, formerly known as lipocortin, is a key protein for assessing glucocorticoid sensitivity. Modulated by glucocorticoids, annexin-A1 mediates their anti-inflammatory effects on the innate immune system and participates in the negative feedback on adrenocorticotropic hormone (ACTH) release by the pituitary, thus regulating cortisol.[19,20] Annexin-A1 inhibits several steps in the inflammatory cascade, enhancing the anti-inflammatory effects of glucocorticoids.[18,21] Present in saliva in response to free cortisol, annexin-A1 provides a noninvasive biomarker for measuring glucocorticoid sensitivity.[19] This prospective study aims to identify individual factors influencing dexamethasone effectiveness in rebound pain prevention after axillary peripheral nerve block, with a focus on preoperative clinical factors (severe anxiety, pain) and biological factors (salivary cortisol and annexin-A1).

Methods

This was a single-centre prospective study conducted at Cliniques Universitaires St. Luc (Brussels, Belgium) adhering to the ethical principles of the Helsinki Declaration. The protocol was approved by the local ethical committee (ref. 2022/28SEP/358) and was registered on ClinicalTrials.gov before patient recruitment (NCT05763433).

Recruitment

Outpatients aged 18–75 yr undergoing elective upper limb surgery (at or distal to the elbow) under single-shot axillary brachial plexus block were included between April 2023 and April 2024 (Supplementary material). Patients provided written informed consent during the preoperative visit.

Exclusion criteria were patient refusal, contraindications to intraoperative dexamethasone administration or postoperative analgesic use (nonsteroidal anti-inflammatory drugs [NSAIDs], paracetamol), pregnancy, diabetes mellitus, chronic corticosteroid intake, and inability to complete questionnaires. A qualified anaesthetist performed ultrasound-guided blocks, injecting mepivacaine 0.5% (4–5 mg kg^{-1}). Dexamethasone (0.1 mg kg^{-1} i.v.; maximum 10 mg) was administered after the block and before surgical incision. The need for surgical supplementation of the axillary brachial plexus block or administration of systemic drugs such as sedatives, anxiolytics, or hypnotics was considered an exclusion criterion.

Data collection

On the day of surgery, average preoperative pain was assessed using a numeric rating scale (NRS; from 0, no pain to 10, maximal pain). Patients were also asked about recurring preoperative night-time awakening pain in the limb to be operated on. Preoperative medication intake, including analgesics, was recorded.

Patients also completed questionnaires, including the French version of the Pain Catastrophising Scale (PCS; 13 items, score ranging from 0 to 52) to assess negative thoughts related to pain. Patients with scores >18/52 (above the 75th percentile) were classified as high catastrophisers.[22]

Preoperative anxiety was evaluated using a validated French version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS).[23] The APAIS (scored from 6 to 30) is a six-item self-assessment questionnaire that evaluates anxiety on four items (with a score >11 indicating severe anxiety) and information-seeking on two items (a score >8 also suggesting severe anxiety due to the need for information; Appendix 1). The CSI-9, a shortened version of the Central Sensitisation Inventory (CSI), was used to assess somatic and emotional complaints linked to central sensitisation. A score >20 on a 0 to 36 scale identifies central sensitisation.[24] The presence of a neuropathic component in preoperative pain was assessed using the 'Douleur Neuropathique 4' (DN4) questionnaire, with a threshold score of 4 on a 10-point scale.[25] A preoperative blood sample was collected during venous catheter placement to measure levels of high-sensitivity C-reactive protein (hs-CRP) and the neutrophil-to-lymphocyte ratio (NLR) as markers of inflammation.

Before surgery, effectiveness of the axillary brachial plexus block was assessed with a cold test across the different nerve territories. Two orthopaedic surgeons (OB and XL) performed the procedures, all of which were conducted under axillary brachial plexus block alone.

Postoperative care

Postoperative pain management was standardised. In the recovery room, all patients received an oral dose of ibuprofen and paracetamol. If the postoperative pain score (NRS) exceeded 4/10, the patient received 2 mg kg^{-1} of tramadol i.v. Patients were given instructions for managing pain after discharge: 400 mg ibuprofen every 6 h, up to 3 g of paracetamol per day, and oral tramadol as needed.

All patients were contacted by phone at 1, 4, and 30 days and at 3 months after surgery by a research nurse. During each call, postoperative pain intensity was assessed, including average and maximum daily pain and nocturnal pain intensity (NRS, 0–10). Rebound pain was defined as initial mild pain (<4/10) when the patient left the recovery room, progressing to severe pain (>7/10) (NRS, 0–10) occurring within the first hours after resolution of the axillary brachial plexus block, typically 12 to 24 h after the procedure. The rebound pain threshold was based on two recent prospective studies focusing on rebound pain in upper limb surgeries under axillary brachial plexus block.[7,26]

Preoperative saliva analysis of annexin-A1 and cortisol

For each patient, whole saliva was collected between 08:00 and 11:00 using a standard Salivette tube (Sarstedt, Lower Saxony, Germany) following the manufacturer's instructions. After collection, the saliva sample was centrifuged and stored at −80°C until analysis.

Annexin-A1 and cortisol levels were measured in saliva samples using the Invitrogen™ Human ANXA-1 ELISA Kit and the Human Cortisol ELISA Kit (Thermo Fisher Scientific, Waltham, MA, USA). The analyses were performed according to the manufacturer's protocols without modification. Enzyme-linked immunosorbent assay (ELISA) data were analysed using a microplate reader (absorbance at 450 nm) and curve-fitting software to generate standard curves for annexin-A1 and cortisol.

Given the variability in salivary cortisol thresholds reported in the literature based on laboratory standards and detection methods, we selected a normal range of 1150–4160 pg ml^{-1} (25th–75th percentile). For annexin-A1, in the absence of precise data in the literature, the analysis focused on trends and correlations without arbitrary thresholds, to optimise statistical sensitivity.

Statistical analyses and power analysis

Statistical analysis was performed using IBM SPSS Statistics (version 29.0.1.0; Armonk, NY, USA), and results are presented as proportions and means (SD). Parametric data were compared using the Student *t*-test, whereas nonparametric data were analysed using the Mann–Whitney test. Categorical variables were assessed using χ^2 test or Fisher's exact test. A *P*-value <0.05 was considered statistically significant. A univariate logistic regression model was used to assess the association between rebound pain and preoperative risk factors, with inclusion criteria of a $P<0.1$ in χ^2 or Mann–Whitney tests.

Considering an observed proportion of 23% of patients experiencing rebound pain, we estimated a medium effect size for logistic regression with five predictive variables.[6] To achieve a significance level of 0.05 and a power of 0.80, a minimum of 91 participants was required for inclusion in the study.

Results

Of the 138 eligible patients scheduled for upper limb surgery under peripheral nerve block, data from 104 participants were analysed (Supplementary material). Participant characteristics are reported in Table 1. Thirty-six participants (34.6%) developed rebound pain. Preoperative night-time awakening pain (P=0.01), severe anxiety (P=0.02), and low salivary cortisol levels (<1150 pg ml^{-1}, P=0.02) were associated with the occurrence of rebound pain (Table 2). No significant relationship was found with hs-CRP levels or the NLR ratio. Among participants with low salivary cortisol (<1150 pg ml^{-1}), nine (64%) developed rebound pain, whereas five (36%) did not (P=0.02) (Table 2). The Mann–Whitney test revealed no statistically significant correlation between preoperative annexin-A1 levels and rebound pain occurrence (P=0.06). The boxplots (Fig. 1a and b) show a lower median and reduced dispersion of annexin-A1 and cortisol levels in the rebound pain+ group compared with the rebound pain− group. Factors showing a significant relationship with rebound pain occurrence ($P<0.05$) were included in the regression analysis (Table 3).

Multivariable analysis identified severe anxiety (odds ratio [OR]=3.54, P=0.01), night-time awakening pain (OR=3.09, P=0.03), low salivary cortisol (OR=3.33, P=0.02), and high catastrophising score (OR=4.14, P=0.01) as significant predictors of rebound pain (Table 4).

Finally, at 3 months post-surgery, 28 participants (27%) reported chronic pain (NRS >4/10). Among them, 14 belonged to the rebound pain+ group (14/36, 38.9%), whereas 14 (14/68, 20.6%) were from the rebound pain− group (P=0.04).

Discussion

Although all participants in our study received intraoperative dexamethasone (0.1 mg kg^{-1} i.v.), 35% still exhibited rebound pain when their axillary brachial plexus block resolved. Three significant risk factors emerged from the screening of preoperative clinical parameters: high anxiety scores, high catastrophising score, and nocturnal awakening pain. Additionally, participants with low salivary cortisol and annexin-A1 levels were more likely to experience rebound pain when their block resolved despite dexamethasone administration.

Our findings are of clinical interest for two principal reasons. Firstly, the results highlight the lack of preventive effect of dexamethasone against rebound pain in some patients, with the phenotypes identified here. Secondly, our findings contribute to a better understanding of rebound pain mechanisms, which remain poorly understood.

Preoperative anxiety levels were assessed in our patients using two tools: the APAIS (evaluating acute preoperative anxiety) and the PCS (measuring anxiety related to pain perception). High scores on the PCS and the APAIS

Table 1 Participant characteristics. Results are expressed as mean (standard deviation) unless otherwise indicated (median [25th–75th percentile]). Bone surgery: including fractures and trapeziectomies, excluding any soft tissue surgery, cyst excision, and tendon interventions. The absolute difference in salivary annexin-A1 levels between the rebound pain+ and rebound pain− groups was 29.5 ng ml^{-1} (~41.3% of the overall mean). APAIS, Amsterdam Preoperative Anxiety and Information Scale; CSI-9, Central Sensitisation Inventory, nine items; hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PCS, Pain Catastrophising Scale; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment.

	n=104
Sex (female) (*n*)	59 (56.7%)
Age (yr)	49.6 (20-74)
Rebound pain (*n*)	36 (34.6%)
Bone surgery	62 (59.6%)
CSI-9 score (0–36)	20.5 (7)
Preoperative APAIS score (6–30)	12.6 (6.1)
PCS score (0–52)	13.2 (11.6)
Preoperative NTAP* (*n*)	13 (12.5%)
BMI score (kg m^{-2})	25.5 (4.4)
Preoperative hs-CRP (mg L^{-1})	5.5 (23.7)
Preoperative NLR score	2.3 (1.0)
Salivary annexin-A1 (ng ml^{-1})	71.4 (45.4–108.2)
Salivary cortisol (pg ml^{-1})	2270 (1150–4160)

* NTAP: Night-time awakening pain.

questionnaire were predictive of reduced dexamethasone efficacy in preventing rebound pain. Thus, high levels of preoperative anxiety, including pain perception-related anxiety, that is, catastrophising, might be a reliable indicator of reduced glucocorticoid responsiveness. These conditions, often underestimated or overlooked, ideally require time and sometimes specialised follow-up (psychologist, psychiatrist, etc.) for optimal therapeutic management. APAIS was a particularly relevant choice for the questionnaire used to measure preoperative anxiety, not only because of its simplicity and easy clinical use, but also because it specifically evaluates preoperative anxiety related to stress in a surgical context. Other anxiety scales, such as the State–Trait Anxiety Inventory (STAI) score, have been validated in various clinical contexts.[27] The STAI provides a comprehensive assessment of anxiety, encompassing both current emotional responses and chronic vulnerability to anxiety. However, use of STAI requires more time for completion and interpretation, posing challenges in the clinical setting.[27]

Salivary cortisol measurements were included to assess the impact of factors such as chronic stress or chronic pro-inflammatory conditions on glucocorticoid resistance.[16,28,29] Although stress typically elevates cortisol levels, recent research has identified a paradoxical effect where chronic stress (e.g. in post-traumatic stress disorder or burnout) leads to reduced cortisol secretion (i.e. hypocortisolism) owing to the hypothalamic–pituitary–adrenal axis dysregulation. Univariate and multivariate analyses showed an association between low salivary cortisol levels (<1150 pg ml^{-1}) and increased rebound pain risk despite dexamethasone administration.

Persistent pro-inflammatory conditions can induce glucocorticoid resistance through several mechanisms such as reduced histone deacetylase-2 expression and elevated macrophage migration inhibitory factor levels.[17] In our study, we assessed pro-inflammatory status both clinically and biologically. Classical markers such as hs-CRP and the NLR score showed no significant correlation with dexamethasone response, which might be explained by the lack of specificity of systemic markers to reflect the complexity of perioperative inflammation, particularly the localised inflammatory reaction at the surgical site.[30,31] Similarly, obesity, associated with low-grade chronic inflammation, did not appear to be a risk factor for reduced dexamethasone preventive effect in our patients, which is consistent with a similar study that failed to demonstrate reduced glucocorticoid sensitivity in obese patients.[32] In contrast, preoperative nocturnal awakening pain, caused by localised inflammation at the future surgical site, was associated with reduced treatment efficacy. Nocturnal pain, potentially related to night-time cortisol decline, could reactivate inflammatory processes, worsening pain and disrupting sleep.[33]

Fowkes and colleagues[19] reported a positive correlation between salivary cortisol and annexin-A1 levels. In our study,

Table 2 Impact of preoperative factors on rebound pain (rebound pain+): rates with and without the presence of the preoperative factor. Bone surgery: including fractures and trapeziectomies, excluding any soft tissue surgery, cyst excision, and tendon interventions. Severe preoperative anxiety is an anxiety score >10, an information need score >8, or both on the APAIS. APAIS, Amsterdam Preoperative Anxiety and Information Scale; CSI-9, Central Sensitisation Inventory, nine items; DN4, Douleur Neuropathique 4 (neuropathic pain score); hs-CRP, high-sensitivity C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PCS, Pain Catastrophising Scale; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment. *P<0.05.

Preoperative factor	Rebound pain+ with factor (%)	Rebound pain+ without factor (%)	χ^2 value	P-value
Sex (female)	38.9	28. 8	1.15	0.28
Bone surgery	38.7	28.5	1.14	0.28
Positive central sensitisationCSI-9 score ≥20	38.4	30.7	0.68	0.40
Severe preoperative anxietyAPAIS score	50	27.1	5.50	0.02*
High catastrophising scorePCS score >18	54.1	29.1	3.62	0.06
BMI >30 kg m^{-2}	33.3	34.8	0.16	0.90
hs-CRP >3 (mg L^{-1})	42.8	31.5	1.10	0.20
NLR score >2.5	25	38.1	1.50	0.20
Preoperative NTAP	53.5	27.6	6.08	0.01*
Salivary cortisol <1147 (pg ml^{-1})	52	29	6.10	0.02*
Salivary cortisol >4160 (pg ml^{-1})	40.7	32.4	0.61	0.42
DN4 score >4	36.8	34.5	0.37	0.80

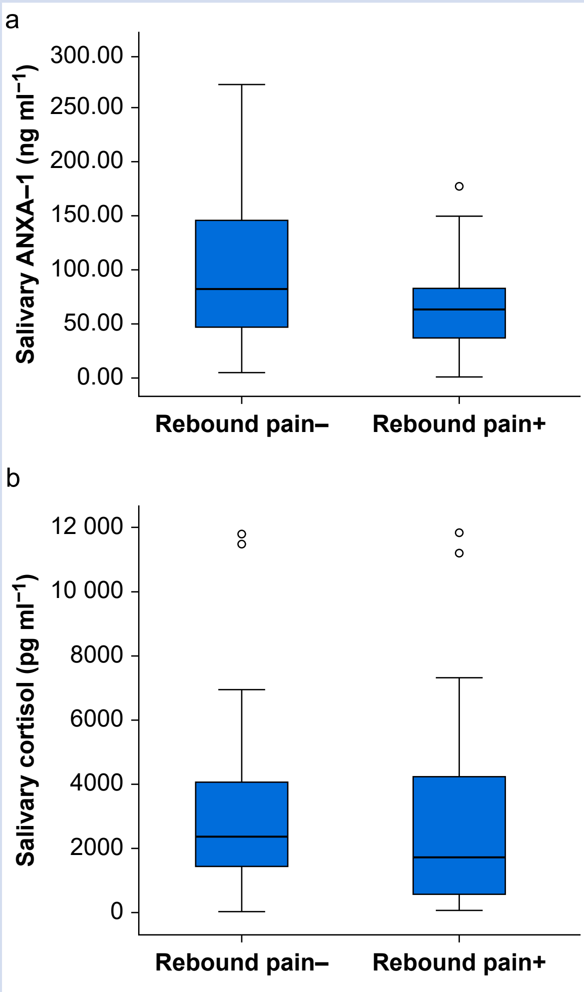

Fig 1. Distribution of preoperative salivary annexin-A1 and cortisol levels based on the occurrence of rebound pain in patients. (a) Distribution of preoperative salivary annexin-A1 concentrations in patients with (+) and without (–) rebound pain. (b) Distribution of preoperative salivary cortisol concentrations in patients with (+) and without (–) rebound pain.

Table 3 Univariate logistic regression analysis of rebound pain occurrence based on preoperative factors. Severe preoperative anxiety is an anxiety score >10, an information need score >8, or both on the Amsterdam Preoperative Anxiety and Information Scale. The regression coefficient for annexin-A1 levels was negative in univariate analysis. Linear regression analysis reveals a significant interaction between salivary annexin-A1 and cortisol (B=0.06, P<0.001), with no excessive colinearity (variance inflation factor=1.00). B, Logistic regression coefficient; CI, confidence interval; OR, odds ratio; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment; PCS, Pain Catastrophising Scale. *P<0.05.

	B	OR	95% CI	P-value
Preoperative NTAP	1.106	3.02	1.23–7.41	0.02*
High catastrophisers (PCS score >18)	0.829	2.29	0.90–5.82	0.08
Severe preoperative anxiety	1.335	2.68	1.14–6.31	0.02*
Low salivary cortisol (<1150 pg ml^{-1})	1.09	2.97	1.19–7.41	0.02*
Salivary annexin-A1 concentration (ng ml^{-1})	−0.01	0.99	0.98–0.99	0.03*

low annexin-A1 and cortisol levels were associated with reduced dexamethasone efficacy in preventing rebound pain. Annexin-A1 is a key marker of glucocorticoid sensitivity, acting as a mediator of anti-inflammatory effects by reducing neutrophil migration.[19,34,35] Low cortisol levels have been linked to downregulation of dexamethasone sensitivity in leucocytes, that is, reduced inhibition of pro-inflammatory cytokine release.[13] Because annexin-A1 is a marker of glucocorticoid sensitivity, low levels might reduce the efficacy of both endogenous and exogenously administered glucocorticoid.[19] In individuals with low annexin-A1 levels, increased neutrophil infiltration associated with enhanced release of pro-inflammatory mediators at the surgical site could exacerbate local inflammation, increasing the risk of rebound pain despite dexamethasone administration.

Among the mechanisms underlying the rebound pain phenomenon, an exacerbated local inflammatory reaction at the surgical site, facilitated by vasodilation induced by the peripheral nerve block, has been proposed.[2,36] I.V. dexamethasone administration reduces the incidence of rebound pain (15% *vs* 44%) and is also associated with decreased postoperative release of pro-inflammatory cytokines (interleukin [IL]-1β, IL-6, and tumour necrosis factor-α [TNF-α]).[37] Although both i.v. and perineural dexamethasone reduce rebound pain, i.v. dexamethasone appears to be more effective.[8,9] In a study comparing the preventive effect of 5 mg dexamethasone administered intravenously or perineurally during interscalene plexus block, the duration of analgesia and the onset of rebound pain were longer in the perineural group, whereas the incidence of rebound pain was lower in the i.v. dexamethasone group (20% *vs* 44%).[38] These findings suggest a more potent anti-inflammatory effect of i.v. dexamethasone compared with that of perineural dexamethasone, which is likely attributable to secondary systemic drug absorption. Accordingly, in the large retrospective study of Barry and colleagues,[1] duration of sensory block was not associated with the incidence or severity of rebound pain.

Finally, our results suggest an association between postoperative rebound pain and the persistence of pain at 3 months after surgery. Although the study was not designed to explore the relationship between rebound pain and chronic postsurgical pain, the findings underline the link between acute postoperative pain intensity and a potential progression to chronic pain.[39] Therefore, optimising rebound pain prevention could help reduce the risk of chronic postoperative pain, particularly in the setting of orthopaedic procedures where more than half of patients report long-lasting pain beyond 3 months.[40]

In personalised medicine, identifying predictive factors of therapeutic effectiveness can guide clinical management. At-risk patients could benefit from enhanced monitoring, improved education on analgesia, and customised analgesic strategies. Increasing the dexamethasone dose could also be

Table 4 Significant risk factors associated with the occurrence of rebound pain by multivariate logistic regression. Severe preoperative anxiety is an anxiety score >10, an information need score >8, or both on the Amsterdam Preoperative Anxiety and Information Scale. The regression coefficient for annexin-A1 levels was negative in multivariate analysis. Linear regression analysis reveals a significant interaction between salivary annexin-A1 and cortisol (B=0.06, P<0.001), with no excessive colinearity (variance inflation factor=1.00). B, logistic regression coefficient; CI, confidence interval; OR, odds ratio; preoperative NTAP, night-time awakening pain as reported by the patient during the preoperative assessment; PCS, Pain Catastrophising Scale. *P<0.05.

	Adjusted B	Adjusted OR	95% CI	P-value
Preoperative NTAP	1.13	3.09	1.13–7.65	0.03*
High catastrophisers (PCS score >18)	1.42	4.14	1.32–12.99	0.01*
Severe preoperative anxiety	1.26	3.54	1.31–9.55	0.01*
Salivary cortisol (<1150 pg ml^{-1})	1.20	3.33	1.17–9.50	0.02*
Salivary annexin-A1 concentration (ng ml^{-1})	−0.01	0.99	0.98–0.99	0.02*

considered for patients with specific preoperative risk factors. Although our results suggest that low cortisol levels reduce dexamethasone efficacy, a higher dose might paradoxically benefit high-risk patients. Indeed, one study reported a lower incidence of rebound pain (9%) in a similar setting with a dexamethasone dose of 16 mg, twice the dose used in our study (34.6% rebound pain).[7] Given the potential side-effects of glucocorticoids (e.g. hyperglycaemia, infection risks), targeting patients who could benefit from higher doses would be appropriate.[5] Future studies should assess the potential benefits of higher dexamethasone doses to prevent rebound pain in patients with high preoperative anxiety, high catastrophising, and severe nocturnal pain.

Strengths and limitations

This study is the first to explore the variability in dexamethasone efficacy for rebound pain prevention. Several methodological limitations must be acknowledged. Saliva samples were collected in the morning without standardised timing, which could introduce bias due to diurnal cortisol variation. Additionally, we assessed baseline cortisol levels using a single measurement, without repeated measures or stress assessments, and we did not perform stress or ACTH challenge. Our results suggest that annexin-A1 could be a useful biomarker for predicting the effectiveness of dexamethasone in preventing rebound pain. However, saliva analysis requires specialised expertise and infrastructure, limiting its regular clinical use. Moreover, we did not assess blood pro-inflammatory cytokine release in patients with or without rebound pain, nor did we correlate it with salivary annexin-A1 levels. Finally, the absence of a control group without dexamethasone administration could limit our findings on dexamethasone efficacy in subgroup analysis.

In conclusion, this study highlights the variability in the efficacy of i.v. dexamethasone in preventing rebound pain. Limited efficacy was related to specific individual preoperative factors such as severe anxiety, high catastrophising, nocturnal pain, and reduced salivary cortisol levels. These results also support the hypothesis that the extent of the local inflammation caused by surgical trauma and exacerbated by peripheral nerve block is a major mechanism underlying the rebound pain phenomenon.

Authors' contributions

Study conception and design: NTDG
Research ethics board application and maintenance, writing the manuscript: NT
Data collection: NTAPXL
Statistical analysis: JLG
Reviewing and approval of the manuscript: all authors

Acknowledgements

We would like to thank L. Miltoni and M. Momeni (Cliniques Universitaires Saint-Luc, Brussels) for statistical assistance and N. Chibani and O. Nyabi (Université Catholique de Louvain [Laboutarie], Brussels) for their help in data analysis.

Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2025.05.055.

Amsterdam Preoperative Anxiety and Information Scale (APAIS): List of Six Items

Original items	French items
1. I am worried about anaesthesia	Je suis inquiet à propos de mon anesthésie
2. The anaesthesia is constantly on my mind	Je pense continuellement à mon anesthésie
3. I would like to know as much as possible about anaesthesia	Je désire savoir tout ce qui est possible à propos de mon anesthésie
4. I am worried about the procedure	Je suis inquiet(e) à propos de mon opération
5. The procedure is constantly on my mind	Je pense continuellement à mon opération
6. I would like to know as much as possible about the procedure	Je désire savoir tout ce qui est possible à propos de mon opération

Appendix 1.

The APAIS is a six-item self-assessment questionnaire. Each element is rated from 1 (‘not at all’) to 5 (‘extremely’). Four items assess anxiety (the patient with a score ≥11 is considered to be very anxious), and two items assess the desire for information (the patient with a score >8 is considered to be very anxious because there is a correlation between the need for information and anxiety). The score may range from 6 (‘no anxiety’) to 30 (‘very anxious’).
From Maurice-Szamburski A, Loundou A, Capdevila X, Bruder N, Auquier P. Validation of the French version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS). *Health Quality Life Outcomes* 2013; **11**: 166.

References

1. Barry GS, Bailey JG, Sardinha J, Brousseau P, Uppal V. Factors associated with rebound pain after peripheral nerve block for ambulatory surgery. *Br J Anaesth* 2021; **126**: 862–71
2. Lavand’homme P. Rebound pain after regional anesthesia in the ambulatory patient. *Curr Opin Anaesthesiol* 2018; **31**: 679–84
3. Dada O, Gonzalez Zacarias A, Ongaigui C, et al. Does rebound pain after peripheral nerve block for orthopedic surgery impact postoperative analgesia and opioid consumption? A narrative review. *Int J Environ Res Public Health* 2019; **16**: 3257
4. Myles PS, Corcoran T. Benefits and risks of dexamethasone in noncardiac surgery. *Anesthesiology* 2021; **135**: 895–903
5. Baeriswyl M, Kirkham KR, Jacot-Guillarmod A, Albrecht E. Efficacy of perineural vs systemic dexamethasone to prolong analgesia after peripheral nerve block: a systematic review and meta-analysis. *Br J Anaesth* 2017; **119**: 183–91
6. Touil N, Pavlopoulou A, Delande S, et al. Effect of intravenous dexamethasone dose on the occurrence of rebound pain after axillary plexus block in ambulatory surgery. *J Clin Med* 2023; **12**: 4310
7. Holmberg A, Hassellund SS, Draegni T, et al. Analgesic effect of intravenous dexamethasone after volar plate surgery for distal radius fracture with brachial plexus block anaesthesia: a prospective, double-blind randomised clinical trial. *Anaesthesia* 2020; **75**: 1448–60
8. Singh NP, Makkar JK, Chawla JK, Sondekoppam RV, Singh PM. Prophylactic dexamethasone for rebound pain after peripheral nerve block in adult surgical patients: systematic review, meta-analysis, and trial sequential analysis of randomised controlled trials. *Br J Anaesth* 2024; **132**: 1112–21
9. Yang ZS, Lai HC, Jhou HJ, Chan WH, Chen PH. Rebound pain prevention after peripheral nerve block: a network meta-analysis comparing intravenous, perineural dexamethasone, and control. *J Clin Anesth* 2024; **99**, 111657
10. Munirama S, McLeod G. ‘Stratified’ approach to individualized anaesthetic care. *Br J Anaesth* 2015; **114**: 543–5
11. Wirtz PH, Elsenbruch S, Emini L, Rüdisüli K, Groessbauer S, Ehlert U. Perfectionism and the cortisol response to psychosocial stress in men. *Psychosom Med* 2007; **69**: 249–55
12. Eller-Smith OC, Nicol AL, Christianson JA. Potential mechanisms underlying centralized pain and emerging therapeutic interventions. *Front Cell Neurosci* 2018; **12**: 35
13. Lekander M, Axén J, Knutsson U, et al. Cytokine inhibition after glucocorticoid exposure in healthy men with low versus high basal cortisol levels. *Neuroimmunomodulation* 2009; **16**: 245–50
14. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; **313**: 2456–73
15. Owen CE, McMaster C, Liew DFL, Leung JL, Scott AM, Buchanan RRC. Neutrophil to lymphocyte ratio predicts glucocorticoid resistance in polymyalgia rheumatica. *Int J Rheum Dis* 2021; **24**: 56–62
16. Fries E, Hesse J, Hellhammer J, Hellhammer DH. A new view on hypocortisolism. *Psychoneuroendocrinology* 2005; **30**: 1010–6
17. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. *Lancet* 2009; **373**: 1905–17
18. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin Sci (Lond)* 1998; **94**: 557–72
19. Fowkes RC, Moradi-Bidhendi N, Brancaleone V, et al. Annexin-a1 protein and its relationship to cortisol in human saliva. *Psychoneuroendocrinology* 2013; **38**: 722–7
20. Yilmaz M, Bal İ, Hanli S, Turkmen E, Balci N, Toygar HU. Annexin levels in gcf determine the imbalance of periodontal inflammatory regulation. *Sci Rep* 2024; **14**, 28833
21. Perretti M, D’Acquisto F. Annexin a1 and glucocorticoids as effectors of the resolution of inflammation. *Nat Rev Immunol* 2009; **9**: 62–70
22. Touil N, Pavlopoulou A, Barbier O, Libouton X, Lavand’homme P. Evaluation of intraoperative ketamine on the prevention of severe rebound pain upon cessation of peripheral nerve block: a prospective randomised, double-blind, placebo-controlled study. *Br J Anaesth* 2022; **128**: 734–41
23. Maurice-Szamburski A, Loundou A, Capdevila X, Bruder N, Auquier P. Validation of the French version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS). *Health Qual Life Outcomes* 2013; **11**: 166
24. Tanaka K, Nishigami T, Mibu A, et al. Cutoff value for short form of central sensitization inventory. *Pain Pract* 2020; **20**: 269–76
25. Bouhassira D, Attal N, Alchaar H, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005; **114**: 29–36
26. Fang J, Shi Y, Du F, et al. The effect of perineural dexamethasone on rebound pain after ropivacaine single-injection nerve block: a randomized controlled trial. *BMC Anesthesiol* 2021; **21**: 47
27. Kassahun WT, Mehdorn M, Wagner TC, Babel J, Danker H, Gockel I. The effect of preoperative patient-reported anxiety on morbidity and mortality outcomes in patients undergoing major general surgery. *Sci Rep* 2022; **12**: 6312
28. Heim C, Ehlert U, Hellhammer DH. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology* 2000; **25**: 1–35
29. Yehuda R. Sensitization of the hypothalamic-pituitary-adrenal axis in posttraumatic stress disorder. *Ann N Y Acad Sci* 1997; **821**: 57–75
30. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003; **111**: 1805–12

31. Biswas M, Suvarna R, Krishnan SV, Devasia T, Shenoy Belle V, Prabhu K. The mechanistic role of neutrophil lymphocyte ratio perturbations in the leading non communicable lifestyle diseases. *F1000Res* 2022; **11**: 960
32. Jönsson S, Lundberg AK, Chung RWS, Jonasson L. Glucocorticoid sensitivity and inflammatory status of peripheral blood mononuclear cells in patients with coronary artery disease. *Ann Med* 2018; **50**: 260–8
33. Sipilä RM, Kalso EA. Sleep well and recover faster with less pain – a narrative review on sleep in the perioperative period. *J Clin Med* 2021; **10**: 2000
34. Mulla A, Leroux C, Solito E, Buckingham JC. Correlation between the antiinflammatory protein annexin 1 (lipocortin 1) and serum cortisol in subjects with normal and dysregulated adrenal function. *J Clin Endocrinol Metab* 2005; **90**: 557–62
35. Allcock GH, Allegra M, Flower RJ, Perretti M. Neutrophil accumulation induced by bacterial lipopolysaccharide: effects of dexamethasone and annexin 1. *Clin Exp Immunol* 2001; **123**: 62–7
36. Yamada T, Hasegawa-Moriyama M, Kurimoto T, Saito T, Kuwaki T, Kanmura Y. Peripheral nerve block facilitates acute inflammatory responses induced by surgical incision in mice. *Reg Anesth Pain Med* 2016; **41**: 593–600
37. Gao M, Li Y, Yu J, et al. The effects of intravenous dexamethasone on rebound pain after nerve block in patients with ankle fracture: a randomized controlled trial. *J Pain Res* 2023; **16**: 1127–36
38. Lee HJ, Woo JH, Chae JS, Kim YJ, Shin SJ. Intravenous versus perineural dexamethasone for reducing rebound pain after interscalene brachial plexus block: a randomized controlled trial. *J Korean Med Sci* 2023; **38**, e183
39. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother* 2009; **9**: 723–44
40. Fuzier R, Rousset J, Bataille B, Salces-y-Nédéo A, Maguès JP. One half of patients reports persistent pain three months after orthopaedic surgery. *Anaesth Crit Care Pain Med* 2015; **34**: 159–64

Handling Editor: Hugh C Hemmings Jr