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Clinical Investigation

CLINICAL INVESTIGATION

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

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Abstract

Background: Pain after resolution of peripheral nerve block, known as 'rebound pain' (RP), is a major problem in outpatient surgery. The primary objective was to evaluate the benefit of intraoperative ketamine at an anti-hyperalgesic dose on the incidence of rebound pain after upper limb surgery under axillary plexus block in ambulatory patients. The secondary objective was to better understand the rebound pain phenomenon (individual risk factors).

Methods: In this prospective, double-blind study, patients were randomised to receive either a single dose of i.v. ketamine (0.3 mg kg^{-1}) or a placebo. Preoperative mechanical temporal summation and central sensitization inventory were applied to question underlying central sensitisation. Pain catastrophising and Douleur Neuropathique 4 questionnaires were used. Rebound pain was defined as pain intensity score >7 (numeric rating scale, 0–10) after block resolution. Postoperative pain was recorded at Days 1, 4, and 30 after discharge.

Results: A total of 109 subjects completed the study, and 40.4% presented with rebound pain. Ketamine administration did not reduce rebound pain incidence or intensity. Temporal summation and central sensitisation inventory scores did not differ between subjects with and without rebound pain. The predictive risk factors were bone surgery (odds ratio [OR]=5.2; confidence interval [CI], 1.9–14.6), severe preoperative pain (OR=4.2; CI, 1.5–11.7), and high pain catastrophising (OR=4.8; CI, 1.0–22.3). At Day 30, the average daily pain was higher in the rebound pain group involving neuropathic characteristics.

Conclusion: Ketamine at an anti-hyperalgesic dose showed no benefit on rebound pain development. Although central sensitisation might not be involved, preoperative pain intensity, and catastrophising stand as risk factors. Because rebound pain remains frequent despite adequate procedure-specific postoperative analgesia, future studies should focus on patient-specific pain management.

Keywords: central sensitization; ketamine; orthopaedic surgery; peripheral nerve block; rebound pain

Editor's key points

- Rebound pain after surgery, that is pain occurring when a peripheral nerve block wears off, is increasingly reported in ambulatory surgery.
- Intraoperative ketamine at single anti-hyperalgesic doses does not prevent rebound pain after upper limb surgery, which questions the role of central sensitisation in rebound pain.
- Rather, the main risk factors for rebound pain include preoperative pain and psychological profile, particularly high catastrophising.

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Almost 50% of orthopaedic procedures are actually performed on an outpatient setting despite the fact that orthopaedic procedures stand among the most painful surgeries.[1] Peripheral nerve blocks (PNBs) are commonly used to offer comfortable surgical conditions associated to reduced recovery time.[2] However, postoperative pain follow-up is generally missing as the block wears off after patient discharge. Previous studies have highlighted the occurrence of important pain during the first 24 h after outpatient surgery and during the first days after hospital discharge.[1] Severe pain which occurs when a peripheral nerve block wears off has been referred to as rebound pain (RP).[3,4] With the development of ambulatory surgery, the problem has recently had renewed interest.[2,5–7] Several studies have reported more RP in patients who received PNB for surgery in contrast with patients who had general anaesthesia.[8,9] Rebound pain, which usually occurs during the first night at home, outside of a controlled healthcare setting, represents a relevant clinical problem. Besides patient suffering and lower satisfaction,[10] RP may also cause unplanned use of medical resources.[9] In the recent literature, RP is generally mentioned as an under-recognised and poorly understood phenomenon.[7,11] Several causes have been hypothesised such as inadequate pre-emptive administration of multimodal analgesia, exaggerated state of hyperalgesia or personal inability to cope with pain.[6,7]

Severe postoperative pain, including RP, occurs despite the use of recommended 'procedure-specific' analgesic treatment, which argues for the development of 'individual-related' pain management. The present study aimed to consider RP on an individual-related basis. Both psychological and physiological mechanisms – that is endogenous pain processing systems – are involved in the intensity of postoperative pain. The presence of exacerbated endogenous excitatory processes (e.g. facilitation of N-methyl-D-aspartate [NMDA] receptor activation) increases postoperative hyperalgesia caused by local tissue injury.[12] Moreover, some individuals who display such a pro-nociceptive pain modulation profile might be at risk to suffer higher pain relative to injury.[13] Ketamine is a non-selective inhibitor of NMDA receptors that displays analgesic, anti-hyperalgesic, and anti-inflammatory properties.[14] Low doses of ketamine may supplement loco-regional analgesic techniques[15,16] and modulate postoperative pain severity.[14] The first aim of the study was to assess the benefit of intraoperative administration of ketamine (at an anti-hyperalgesic dose) on the incidence of RP after upper limb surgery under axillary plexus block. The secondary aim was to determine the incidence of RP after upper limb surgery and to better understand the risk factors associated to its development in ambulatory patients.

Methods

This prospective randomised double-blinded study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Committee of the Cliniques Universitaires Saint-Luc, Brussels, Belgium (Chairperson Professor J.-M. Maloteaux, ref 2019/05JUL/303). The study was registered before the first patient enrolment at www.clinicaltrials.gov (NCT04890418) and Eudract (No: 2019-001079-35).

Recruitment

Patients between 18 and 80 yr of age scheduled for elective ambulatory upper limb surgery (elbow and under) under an axillary plexus block were prospectively enrolled between January 2019 and March 2021. Patients were recruited during preoperative surgical or anaesthesia visit. All subjects participating in the study provided full written informed consent forms.

Exclusion criteria included patient refusal, contraindications to the use of ketamine or to the use of regular postoperative analgesics such as NSAIDs and paracetamol, pregnant or suspected pregnant women, patients with diabetes mellitus and vascular disease, and patients unable to understand the perioperative questionnaires (language problem or cognitive impairment).

Preoperative assessment

The preoperative assessment (at Day 0) investigated preoperative pain at rest, with movement and pain during the previous night at the operative site using a numeric rating scale (NRS) from 0 to 10 (where 0=no pain and 10=worst possible pain) and the regular use of preoperative medications including analgesic drugs. The patients completed the Central Sensitization Inventory (CSI) – 40 questions – to assess key somatic and emotional complaints associated with central sensitisation.[17] The French version of CSI was used. As reported in the literature, a cut-off value of 40 (on the scale from 0 to 100) was used to discriminate patients with a positive CSI before surgery.[17] Pain Catastrophizing Scale (PCS), which assesses negative thinking related to pain (i.e. rumination, magnification, and helplessness), was also completed.[18] The presence of a neuropathic component in pain on the site to be operated was assessed with the use of the Douleur Neuropathique 4 (DN4) questionnaire.[19]

Moreover, the presence of a preoperative mechanical temporal summation (TS), which is considered a clinical correlate of the wind-up phenomenon[20] (i.e. increased reactivity of the endogenous excitatory processes), was evaluated on the volar side of both the operated arm and the contralateral arm as follows: the level of pinprick pain intensity on a NRS score from 0 to 10 was recorded after a single stimulus and then after the last application of a train of 10 mechanical stimuli. The difference between the two NRS scores was calculated as the mechanical TS. The mechanical TS was evoked by application of a 281 g von Frey filament (Stoelting, Woodale, CA, USA). The mechanical stimulus was applied at a frequency of 1 Hz within an area of 1 cm in diameter on the volar forearm.[21]

Study intervention

The procedures of randomisation and double-blinding were carried out by the clinical research unit of the Pharmacy department of the Cliniques Universitaires Saint-Luc. Patients were randomised into two groups and allocated to receive (by slow i.v. injection) either ketamine 0.3 mg kg^{-1} i.v. diluted in 10 ml saline or an equivalent volume of saline 0.9%, after the completion of the axillary plexus block, before the tourniquet placement and the start of surgery. To prevent psychomimetic side-effects related to ketamine administration, all patients also received midazolam 2 mg i.v. before axillary plexus block.

Intraoperative and postoperative treatments

Axillary PNB was performed using real-time ultrasound guidance by an anaesthetist trained in the technique. All patients also received optimal perioperative multimodal analgesic

treatment including intraoperative ketorolac (0.5 mg kg^{-1} i.v.) and paracetamol 1 g. If necessary (i.e. NRS >3/10), postoperative tramadol 2 mg kg^{-1} was administered in the recovery room. Pain-free patients were discharged from hospital with a standard analgesic treatment: NSAIDs (ibuprofen 400 mg/6 h), paracetamol 3 g/24 h and if necessary tramadol as rescue analgesic.

The success of axillary plexus sensory block was evaluated using a cold test (ether test) in the different territories before the surgical incision. If the block was not complete, the anaesthesiologist in charge of the patient added local infiltration to the area concerned under echo guidance. If this was not sufficient, the patient was offered general anaesthesia.

Outcome measurements

Duration of surgery, time of tourniquet use, intraoperative complications and postoperative surgical complications were noted. The duration of the axillary block was recorded, and the different phases of its resolution were measured as follows (according to the patient's report on his/her pain diary): time of block completion (H1, day and time), beginning of the occurrence of paraesthesia reported by the patient (H2, day and time after block) and finally the onset of pain at surgery site (H3, day and time after block). At the time the axillary block totally wore off, the patient was told to write the pain intensity felt (NRS, 0–10) in a pain diary provided before hospital discharge.

Subjects were contacted by phone call on Days 1, 4, and 30 after surgery by a research nurse. Postoperative pain intensity was assessed as daily average and maximal pain (NRS, 0–10) and pain intensity felt during the night (NRS, 0–10). On Day 30 after surgery, subjects also completed the short form of the Brief Pain Inventory (BPI) to assess the impact of pain on their daily quality of life (sleep quality, mood, analgesics intake).[22]

Finally, the presence of a neuropathic component in early postoperative pain on Days 4 and 30 was evaluated with the application of the DN4 questionnaire.[23]

Statistical analysis

Statistical analysis was performed with SigmaStat 3.5 (Systat Software GmbH, Erkrath Germany). Results were expressed as proportions, mean (standard deviation [SD]) or median value (inter-quartile range) as specified. According to a Kolmogorov–Smirnov normality test, parametric data between the groups were compared using the unpaired Student *t*-test and non-parametric data with the Mann–Whitney rank-sum test. Categorical data were compared using the χ^2 test and Fisher exact test using a two-tailed probability. For correlation analysis, the Pearson correlation test or Spearman rank order correlation test was used. A value of $P<0.05$ was considered significant. The univariate logistic regression model was used to assess the association between RP when the axillary plexus block wore off (dependent variable) and potential risk factors (non-dependent variables). For the univariate regression, preoperative variables found in the analysis between the RP+ group and the RP− group with a *P* value <0.1 were included: bone surgery, severe pain (NRS >7/10) for maximal pain or night pain, positive PCS (>14/52) or high PCS (>26/52), positive CSI score (>40/100).

The sample size was calculated based on the incidence of rebound pain. The presence of RP was defined as pain intensity score >7 (NRS, 0–10) reported by the patient after axillary plexus block resolution. Different definitions of RP are proposed in the current literature.[6] We have used the definition published in a recent large cohort study, that is NRS >7/10.[11]

A retrospective analysis of preliminary data revealed an incidence of 30% of rebound pain. We calculated that in total 104 subjects were needed to detect a 20% reduction in the incidence of rebound pain from a baseline incidence of 30% using two-sided $\alpha=0.05$ with 80% power. We included a total of 110 subjects, taking into account possible dropouts.

Results

A total of 135 patients were assessed for study eligibility, of which 110 met the inclusion criteria and were enrolled in the study (Consolidated Standards of Reporting Trials [CONSORT] flow diagram). The data of 109 subjects who completed the study were analysed. No axillary plexus block had to be converted to general anaesthesia (three subjects reported some discomfort at the surgical incision, and the block was completed with a local infiltration in the nerve territory as previously explained). No subject needed tramadol administration in the recovery room.

Evaluation of the effect of intraoperative ketamine treatment

Among 109 subjects who completed the study, 54 received ketamine and 55 received saline (placebo group) (Table 1). Demographic data were similar between the two groups (Table 1). Preoperative pain scores and results of psychophysical tests (CSI, PCS, TS) did not differ (Table 1). The duration of the axillary plexus block was slightly longer in the placebo group but without clinical relevance. The median value of the pain intensity noted by the subject after the block resolution did not differ between the two groups of treatment ($P=0.203$). Using the RP definition of NRS score ≥7 out of 10 when the analgesic effects of the axillary block wore off, 44 patients presented with RP (44/109, 40.4%). Among these subjects, 18 (18/54, 33%) had received an intraoperative dose of ketamine (Table 1). In the placebo group, 26 patients (26/55, 47%) presented with RB at the resolution of the block ($P=0.438$). The postoperative evolution of the two groups of treatment was similar regarding postoperative pain scores (average daily pain, average maximal pain, and night pain) recorded at Days 1, 4, 7, and 30 (all *P* values >0.05). Finally, analysis of BPI items (at Day 30) and DN4 scores (preoperative, Day 4, and Day 30) did not reveal differences between the groups of treatment (all *P* values >0.05).

Evaluation of rebound pain characteristics and risk factors

The characteristics of the 109 subjects are presented in Table 2. The incidence of RP in this population was 40.4% (44/109) using the definition of severe pain (NRS ≥7/10) at the block resolution. Axillary plexus block was successfully performed in all subjects, but three subjects required supplementary local infiltration (among these three patients, one presented with RP). A significant increase in the incidence of RP was found in the context of bone surgery (61% *vs* 23%, $P=0.03$). Subjects with RP presented significantly higher pain catastrophising score (global score and all sub-scores). In contrast, the psychophysical measures of central sensitisation such as CSI score

Table 1 Intraoperative ketamine: comparison between subjects who received ketamine treatment and subjects who did not. Values are expressed as mean (standard deviation) or median (inter-quartile range). H1–H2: time interval between the time of the end of the block (H1, day and time) and the beginning of the onset of the paraesthesia reported by the patient (H2, day and time after the block). H2–H3: time interval between of time of beginning of the occurrence of paraesthesia reported by the patient (H2, day and time after block) and finally the onset of pain at surgery site (H3, day and time after block). CSI, Central Sensitization Inventory; PCS, Pain Catastrophizing Scale; RP, rebound pain.

	Ketamine group (n=54)	Placebo group (n=55)	P value
Male/female ratio (n)	27/28	25/29	0.848
Age (yr)	51 (16)	52 (18)	0.687
BMI (kg m^{-2})	26 (6)	24 (6.5)	0.055
Bone surgery (n)	20 (37%)	21 (39%)	0.845
Tourniquet duration (min)	27 (17)	26 (17)	0.917
PCS total (0–52)	11 (2.25–23.0)	12 (3.0–23.0)	0.794
Rumination sub-score	4 (0.25–8.0)	4 (0.25–9.75)	0.765
Magnification sub-score	2 (0–4.0)	2 (0–4.0)	0.838
Helplessness sub-score	6 (0–12.5)	5 (1.0–9.75)	0.854
CSI score (0–100)	21 (11.25–33.5)	18.5 (12.0–27.0)	0.806
TS ipsilateral forearm (0–10)	0 (0–1)	0 (0–1)	0.138
TS contralateral forearm (0–10)	0 (0–1)	0 (0–1)	0.279
Preoperative pain			
Average pain (NRS 0–10)	3 (0–5)	2 (0–4)	0.199
Maximal pain (NRS 0–10)	7 (4–8)	4.5 (2–8)	0.185
Night pain (NRS 0–10)	1 (0–5)	0 (0–3)	0.233
Pain when block wear off			
Intensity (NRS 0–10)	6 (4–8)	4.5 (2–8)	0.203
Incidence RP (n)	18 (33%)	26 (47%)	0.438
Axillary block duration			
Total duration (min)	520 (347–720)	630 (510–790)	0.043
H1–H2 duration (min)	345 (215–465)	400 (309–538)	0.044
H2–H3 duration (min)	135 (90–300)	180 (120–300)	0.266

Table 2 Demographic data: comparison between subjects with rebound pain (RP+) and subjects without rebound pain (RP–). Values are expressed as mean (SD) or median (IQR). H1–H2: time interval between the time of the end of the block (H1, day and time) and the beginning of the onset of the paraesthesia reported by the subject (H2, day and time after the block). H2–H3: time interval between of time of beginning of the occurrence of paraesthesia reported by the subject (H2, day and time after block) and finally the onset of pain at surgery site (H3, day and time after block). CSI, Central Sensitization Inventory; DN4, Douleur Neuropathique 4 questionnaire; IQR, inter-quartile range; NRS, numeric rating scale; PCS, Pain Catastrophizing Scale; SD, standard deviation; TS, temporal summation.

	RP+ group (n=44)	RP– group (n=65)	P value
Male/female ratio (n)	16/28	36/29	0.055
Age (yr)	53 (18)	51 (17)	0.617
BMI (kg m^{-2})	26 (6.5)	26 (5)	0.899
Bone surgery (n)	27 (61%)	15 (23%)	0.003
Tourniquet duration (min)	29 (17)	25 (17)	0.278
PCS total (0–52)	16.5 (7–31.5)	7 (2.0–17.0)	0.003
Rumination sub-score	5.0 (1.0–11.5)	3.0 (0–7)	0.029
Magnification sub-score	3.0 (0.5–6)	2.0 (0–3)	0.019
Helplessness sub-score	8.0 (3.0–15.5)	3.0 (0–7)	0.001
CSI score (0–100)	21 (12.5–28)	18 (11–26.5)	0.455
TS ipsilateral forearm (0–10)	0 (0–1)	0 (0–1)	0.501
TS contralateral forearm (0–10)	0 (0–1)	0 (0–1)	0.297
Preoperative pain			
Average pain (NRS 0–10)	4.0 (2.5–5.5)	1.0 (0–3.0)	<0.001
Maximal pain (NRS 0–10)	8.0 (6.5–8.0)	4.0 (0.5–7.0)	<0.001
Night pain (NRS 0–10)	3.0 (0–5.5)	0 (0–2.0)	0.002
DN4 score (0–10)	3.0 (1–4.25)	2.0 (0.25–4)	0.558
Rebound pain			
Intensity (NRS 0–10)	8.5 (7.25–9.75)	3.25 (1–5)	<0.001
Intraoperative ketamine (n)	25 (57%)	29 (45%)	0.438
Axillary block duration			
Total duration (min)	570 (382–748)	612 (465–750)	0.354
H1–H2 duration (min)	357 (222–500)	370 (282–535)	0.406
H2–H3 duration (min)	142 (60–277)	180 (120–330)	0.031

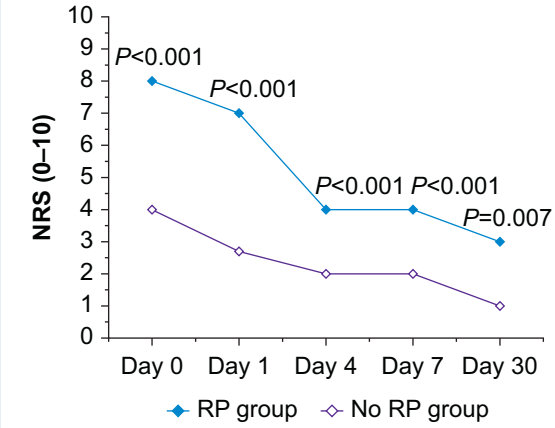

Fig 1. Postoperative evolution of maximal pain between subjects with rebound pain (RP+) and subjects without rebound pain (RP−). NRS, numeric rating scale.

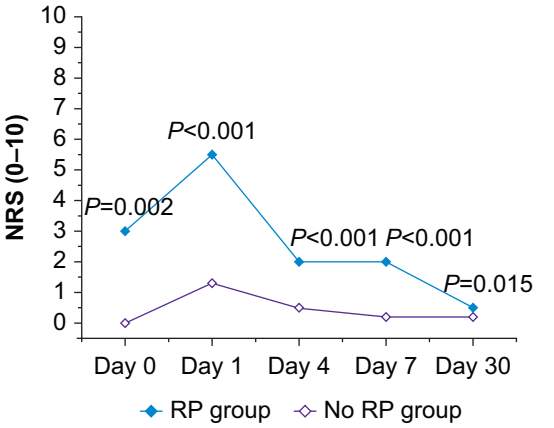

Fig 2. Postoperative evolution of night pain between subjects with rebound pain (RP+) and subjects without rebound pain (RP−). NRS, numeric rating scale.

and TS assessment did not differ between patients with and without RP. Preoperative DN4 also was not different.

Importantly, subjects in the RP group reported significantly higher preoperative pain at the surgical site, for average pain, maximal pain, and night pain (Table 2). Whether the total duration of the axillary block did not differ, the duration of paraesthesia felt by the patient during the block alleviation (H2−H3 interval) was shorter in subjects with RP (P=0.031). Regarding the postoperative evolution, the pain trajectories in patients with RP were significantly higher (i.e. worse pain resolution) for daily maximal pain (Fig. 1), daily average pain, and night pain (Fig. 2) until Day 30. At Day 30, average daily pain was still rated higher in the RP group (P=0.042). However, the impact of pain on the quality of life as assessed by sleep, mood, and life enjoyment did not differ between the two groups. In the RP group, 14% of the patients mentioned regular intake of analgesics (including weak opioids, n=6/44) *vs* 3% (n=2/65) in patients without RP (P=0.059). We note that preoperative opioid intake was significantly higher, that is 20% (9/44) in the RP group *vs* 6% (4/65) in patients without RP (P=0.034). Finally, at Day 30, but not preoperatively nor at Day 2, the DN4 score was higher in patients with RP (median value=2; inter-quartile range [IQR], 1−3) than in patients without RP (median value=1; IQR, 0−2) (P=0.021) although the incidence of positive DN4 scores did not differ between the groups (29% in the RP+ group *vs* 22% in the RP− group, P=0.484).

We found positive correlations between RP intensity and the score of several preoperative psychophysical tests (Table 3) and the 24 h postoperative maximal NRS score questioned at Day 1 (0.729; P=0.0000). Finally, analysis of preoperative CSI revealed the presence of a positive CSI (defined as a value of at least 40/100) in 9% of subjects with RP (4/44) *vs* 9% in subjects without RP (6/65) (n.s.). Regarding pain catastrophising, 50% of subjects with RP (22/44) presented with a score >14 (median value of the full group) *vs* 31% (20/65) in the no RP group (P=0.047). High catastrophisers (i.e. patients in the third percentile, PCS score >26 on the scale from 0 to 52) accounted for 34% (15/44) of the subjects with RP *vs* 11% (7/65) of subjects without RP (P=0.004). The use of multiple logistic regression model highlighted the following risk factors to develop RP after upper limb surgery under axillary plexus block: bone surgery, presence of severe preoperative maximal pain, and high catastrophising (Table 4).

Discussion

To our knowledge, this is one of the rare prospective randomised studies to specifically address the phenomenon of RP including possible mechanism and preventive treatment in ambulatory patients.

Our results did not show any benefit of a single anti-hyperalgesic dose of ketamine (0.3 mg kg^{-1}) as the incidence of RP did not differ between ketamine and placebo groups (47% *vs* 33%), nor did the intensity of RP. Several explanations are possible. First, the failure of single ketamine bolus doses to reduce postoperative pain has been questioned.[14] However, the present setting, that is ambulatory surgery performed in awake patients, precluded the administration of higher or repeated doses of ketamine. Second, multimodal analgesia might have blunted the benefit of ketamine (<0.5 mg kg^{-1}). In studies about low doses of ketamine (0.2−1.0 mg kg^{-1}) to supplement loco-regional analgesia, general anaesthesia was often provided.[15,16] In such context, low doses of ketamine showed a postoperative opioid sparing effect but inconstant reduction on pain scores. Interestingly, one study assessed the effect of ketamine 10 mg i.v. administered in awake patients under spinal anaesthesia during Caesarean delivery.[24] All patients received perioperative multimodal analgesic regimen and the incidence of breakthrough pain during the first 24 h was not reduced (75% *vs* 74% in ketamine and placebo groups, respectively).[24] Third, the lack of ketamine effect might be related to the fact that underlying central sensitisation does not play a major role in RP development. Our assessment of endogenous pain processes by CSI questionnaire and mechanical TS only concerned the pro-nociceptive systems. The CSI global score was similar in patients with and without RP, and the preoperative incidence of positive CSI (score >40) did not differ. Mechanical TS measured on the forearm also did not differ between both groups. Finally, in a large retrospective

Table 3 Pearson's correlations found between the intensity of rebound pain (RP) reported by the patients when the analgesic effect of the block wears off and different preoperative psychophysical tests. CSI, Central Sensitization Inventory; DN4, Douleur Neuropathique 4 questionnaire; PCS, Pain Catastrophizing Scale; RP, rebound pain; TS, temporal summation.

	Preoperative maximal pain	Preoperative average pain	Preoperative night pain	Preoperative DN4 score
RP intensity	0.467* P=0.0000	0.392* P=0.0000	0.313* P=0.002	0.108 P=0.293
	PCS total score	**PCS sub-score helplessness**	**CSI total**	**TS score on operated arm**
RP intensity	0.250* P=0.009	0.294* P=0.002	0.003 P=0.974	0.188 P=0.052

Asterisks highlight statistically significant results (P value <0.05).

study, intraoperative ketamine did not seem to affect the development of RP (40% incidence).[11]

The secondary aim of the present study was to better characterise the phenomenon of RP. Despite the use of procedure-specific multimodal analgesia,[7] RP incidence reached 40% (*n*=44/109), similar to that reported in patients undergoing wrist fracture fixation under PNB both in a prospective study[25] (50% in the placebo group) and a retrospective study[9] (41% in the PNB group *vs* 10% in the general anaesthesia group). Thus, better understanding of mechanisms and predictive risk factors (in other words, 'patient-specific' management) is mandatory. Our results support bone surgery of the upper limb, in contrast to soft tissues surgery, as a major risk factor of RP (odds ratio [OR]=5.2) in agreement with a previous retrospective study (OR=1.8).[11] Female sex and younger age are reported as risk factors of poor postoperative pain control[26] and risk factors of RP.[11] In our study, although female sex almost reached statistical significance (*P*=0.05), age did not probably in relation with exclusion criteria we used, that is diabetes mellitus and vascular diseases, which are more frequent in older patients. We also found preoperative pain intensity to be strongly correlated to RP intensity in agreement with a large retrospective study showing that higher baseline preoperative movement pain scores influenced RP scores.[4] Catastrophisation, an exaggerated negative mental attitude during actual or anticipated pain experience, may predict postoperative pain.[27] Although catastrophisation has been suspected to be associated to RP, no previous study has specifically explored the relationship.[2,6] Using a validated PCS questionnaire, we found that preoperative PCS was higher in patients with RP, the helplessness sub-score being particularly correlated with RP intensity.

Finally, subjects with RP reported higher sub-acute pain at Day 30 although it did not affect their quality of life. Psychological profile, that is high catastrophising, certainly accounts for the higher pain scores reported in subjects with RP. Interestingly, subjects with RP scored higher for DN4 at Day 30. The DN4 questionnaire validity in acute and sub-acute postoperative pain remains debated as the score was only validated in established chronic pain.[28] We hypothetised that neuropathic-like characteristics more likely reflect an exacerbated perioperative inflammatory reaction. Dexamethasone seems able to prevent RP both in experimental conditions[29] and clinical studies.[11,25] Beyond the modulation of perioperative inflammation, dexamethasone significantly prolongs the duration of PNB,[25] a mechanism supposed to reduce the risk of RP.[3,6] We did not find a significant difference in total axillary block duration between patients with and without RP, in agreement with a retrospective study,[4] but the duration of paraesthesia was shorter in patients with RP.

Table 4 Risk factors associated with the development of severe pain (NRS >7/10), that is RP when axillary plexus block wears off in the context of ambulatory upper arm surgery. CSI, Central Sensitization Inventory; NRS, numeric rating scale; PCS, Pain Catastrophizing Scale; RP, rebound pain.

Risk factor	Odds ratio	5% Conf. lower	95% Conf. upper	*P* value
Female sex	0.538	0.201	1.442	0.218
Bone surgery	5.246	1.883	14.619	0.002*
Severe preoperative maximal pain (NRS >7/10)	4.203	1.512	11.683	0.006*
Severe preoperative night pain (NRS >7/10)	0.471	0.102	2.170	0.334
Positive preoperative PCS score (>14/52)	1.021	0.278	3.758	0.975
High preoperative PCS score (>26/52)	4.808	1.036	22.306	0.045*
Positive preoperative CSI score (>40/100)	1.401	0.265	7.399	0.691

Asterisks highlight statistically significant results (P value <0.05)

Strengths and limitations of the study

The present study is one of the largest prospective studies (*n*=109) conducted to date about RP after PNB in ambulatory patients. The study tried to better understand the phenomenon by assessing some mechanisms, that is underlying central sensitised state and the potential anti-hyperalgesic effect of ketamine as a preventive strategy. The methods currently used to measure central sensitisation are probably not sensitive and specific enough to detect mechanisms related to outcomes including the response to specific treatments.[30] For example, CSI has been more strongly associated with psychological factors than psychophysical test results in patients with osteoarthritis.[31] The present study is also one of the very few studies to objectively measure the role of psychological factors such as catastrophisation, which is often suspected to promote RP phenomenon.

The study also has several limitations. RP was defined as NRS reported by the patient when the PNB wore off. Several definitions of RP phenomenon exist, including the one that proposes to substitute 'recall pain' (when the PNB wore off) by the highest pain score during the first 24 h.[11] We have compared recall pain with NRS reported by patients during the Day 1 phone call. Both the intensity (0.729; P=0.000) and incidence of severe pain (NRS >7/10) (0.474; P=0.000) were strongly correlated between recall pain and Day 1 maximal pain. In other words, the definition of RP we used may be acceptable. Among other limitations, we limited postoperative follow up to 30 days and the impact of RP on chronic postsurgical pain (at 3 months and later) was not measured. Finally, the dose of ketamine used was low and not repeated. Nevertheless, in awake patients, the psychomimetic side-effects of ketamine precluded a different use. Finally, as aforementioned, the psychophysical tests used to assess underlying central sensitisation in patients may be questioned as well the use of the DN4 questionnaire in an acute postoperative setting.

In conclusion, this prospective randomised study showed no benefit of a single pre-emptive anti-hyperalgesic dose of ketamine to prevent occurrence or to reduce intensity of RP in ambulatory patients undergoing upper limb surgery. Psychophysical tests (CSI, TS) did not demonstrate the involvement of central sensitisation as risk factor for RP in contrast with the experience of preoperative pain intensity and pain catastrophising. Because RP occurrence still remains frequent despite the use of adequate procedure-specific postoperative analgesia, future studies should focus on patient-specific postoperative pain management.

Authors' contributions

Study conception and design: NT, PL
Grant funding application: PL
Research Ethics Board application and maintenance: NT, PL
Data collection: NT, AP, XL, OB
Writing of paper: NT, PL
Reviewing and approval of paper: NT, AP, OB, XL

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Declarations of interest

NT, AP, and PL have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.11.043.

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