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Opioid-induced hyperalgesia in a mice model of orthopaedic pain: preventive effect of ketamine†

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Background. The aim of this study was to assess the preventative effect of ketamine on the exaggerated postoperative pain observed in sufentanil-treated mice and its ability to improve the analgesic effectiveness of morphine during the postoperative period in an orthopaedic model of pain.

Methods. In this study, we assessed the effects of ketamine on sufentanil enhancement of pain behaviour induced by fracture and the effects of ketamine on postoperative morphine-induced analgesia. Three tests were used to assess pain behaviour: von Frey filament application, hot-plate test, and a subjective pain scale.

Results. When administered 1 day after surgery in mice treated with sufentanil on D0 (before surgery), morphine induced an analgesic effect as observed by the nociceptive threshold increase in saline- and ketamine-treated mice. Morphine was more effective in ketamine-treated (1 and 50 mg kg^{-1}) mice.

Conclusions. Our results suggest that pre-emptive use of ketamine is useful in orthopaedic surgery in this mice model to diminish short- and long-term hyperalgesia, but also to improve morphine effectiveness leading to a better mobilization and more rapid rehabilitation.

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Postoperative pain management is a great challenge because it is a critical part of a patient's recovery.[1 2] Bone injury is often accompanied by acute pain that can be clearly diminished by morphine use.[3 4] However, although opioids are among the most effective analgesics in humans, there is growing evidence showing that they also induce abnormal and prolonged pain states after acute or chronic administration.[5 6] It has been proposed that postoperative pain in patients receiving opioids during surgery could result not only from the nociceptive input related to tissue damage, but also from opioid-induced pain sensitization.[5 7 8] Recently, it was demonstrated that ketamine not only improves exaggerated postoperative incisional pain management, but also provides better postoperative rehabilitation.[9] We recently described a model of fracture pain in mice that could mimic orthopaedic surgery.[3] The aim of this study was to assess the preventative effect of ketamine on the exaggerated postoperative pain observed in sufentanil-treated mice and its ability to improve the analgesic effectiveness of morphine during the postoperative period.

Methods

Animals

This study, including care of the animals involved, was conducted according to the official edict presented by the French Ministry of Agriculture (Paris, France) and the recommendations of the Helsinki Declaration. Thus, these experiments were conducted in an authorized laboratory and under the supervision of an authorized researcher. These experiments were approved by our institutional

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animal care and use committee, and this study was conducted in accordance with the International Association for the Study of Pain guidelines on the use of animals in experimental research.[10] Adult C57 BL/6 male mice (Jackson Laboratories, Bar Harbor, ME, USA) were used in all experiments. The animals were housed individually in isolator cages with solid floor covered with 3 cm of soft bedding and were fed and watered *ad libitum*. Animals were on a 12 h light–dark cycle.

Surgery

All mice were anaesthetized with sevoflurane 1.5–2% in air, delivered via cone nose. The depth of anaesthesia was assessed using withdrawal reflex at the left paw. Closed fracture of the tibia was performed as previously described.[3] Briefly, after antiseptic preparation of the right paw with povidone iodine, a unilateral, closed fracture was produced in the right tibia using a specially designed fracture apparatus (blunt guillotine). For the intramedullary pinning using a sterile technique, a hole was made percutaneously above the tibial tuberosity using a 27 G needle (BD, Drogheda, Ireland). Then the needle was directed directly into the medullary canal. By rotating the needle, the canal was reamed to 5 mm up to the ankle joint. The end of the needle was cut as short as possible, so that the skin could roll over and cover it. No suture was used. Then, the mouse was placed with the leg on the anvil, so that the blunt guillotine lined up with the proximal third of the tibia. The 300 g weight was dropped from a height of 9–10 cm fracturing the tibia shaft. Radiography confirmed the fracture.

Experimental groups

Protocol A: effects of ketamine on sufentanil enhancement of pain behaviour induced by fracture

We studied the early and long-lasting effects of sufentanil on nociceptive threshold using a procedure designed to partly mimic its use in orthopaedic surgery. Sixty mice were separated into six groups. In the control group, saline was injected five times s.c. at 15 min intervals. Surgery was performed as described above before the last injection. In the ketamine group, ketamine (50 mg kg^{-1})[11 12] was injected before saline injection, and then saline was injected four times s.c. at 15 min intervals. Surgery was performed as described above before the last injection. In the sufentanil group, saline was injected before the injection of sufentanil, then sufentanil was injected four times (10 μg kg^{-1} per injection, s.c.) at 15 min intervals, resulting in total doses of 40 μg kg^{-1}. Surgery was performed as described above before the last sufentanil injection. In the sufentanil–ketamine 1 group, ketamine (1 mg kg^{-1}) was injected before the sufentanil injection, then sufentanil was injected four times (10 μg kg^{-1} per injection, s.c.) at 15 min intervals, resulting in a total dose of 40 μg kg^{-1}. Surgery was performed as described above before the last sufentanil injection. In the sufentanil–ketamine 10 group, ketamine (10 mg kg^{-1})[9 13] was injected before the sufentanil injection, then sufentanil was injected four times (10 μg kg^{-1} per injection, s.c.) at 15 min intervals, resulting in a total dose of 40 μg kg^{-1}. Surgery was performed as described above before the last sufentanil injection. In the sufentanil–ketamine 50 group, ketamine (50 mg kg^{-1})[11 12] was injected before the sufentanil injection, then sufentanil was injected four times (10 μg kg^{-1} per injection, s.c.) at 15 min intervals, resulting in a total dose of 40 μg kg^{-1}. Surgery was performed as described above before the last sufentanil injection.

Testing (mechanical stimulation, hot-plate test, and pain rating scale) was performed before the surgery (D−1 and D0), then each 30 min after T0 until 120 min after the fracture, then 4 and 6 h after surgery, and once daily during the first 7 postoperative days after the surgery. Experiments were conducted following a double-blind protocol.

Protocol B: effects of ketamine on postoperative morphine-induced analgesia

Twenty other mice were separated into two groups. In the sufentanil group, saline was injected before the injection of sufentanil, then sufentanil was injected four times (10 μg kg^{-1} per injection, s.c.) at 15 min intervals, resulting in total doses of 40 μg kg^{-1}. Surgery was performed as described above before the last sufentanil injection. In the ketamine group, ketamine (50 mg kg^{-1}) was injected before the sufentanil injection, then sufentanil was injected four times (10 μg kg^{-1} per injection, s.c.) at 15 min intervals, resulting in a total dose of 40 μg kg^{-1}. Surgery was performed as described above before the last sufentanil injection. On postoperative day 1 (D1), mice received morphine 3 mg kg^{-1}.

Testing (mechanical stimulation, hot-plate test, and pain rating scale) was performed before the surgery (D−1 and D0), then 2, 4, and 6 h after surgery, and once daily during the first 7 postoperative days after the surgery. Experiments were conducted following a double-blind protocol. On D1, testing was performed before morphine administration then 30 and 90 min after morphine administration.

Behavioural measurements

Three tests were used to assess pain behaviour: (i) mechanical nociception assessed by the withdrawal response to von Frey filament application, (ii) thermal nociception assessed by the withdrawal response to thermal stimulus (hot-plate test), and (iii) subjective pain determined using a pain rating scale as described by Attal and colleagues.[14]

Mechanical nociception

Unrestrained mice were placed beneath a clear plastic chamber on an elevated mesh floor and allowed to acclimatize. Withdrawal responses to mechanical stimulation were determined using calibrated von Frey filaments applied from underneath the cage through openings in the plastic mesh floor against the hindpaw plantar skin at approximately the middle of the fractured leg. The

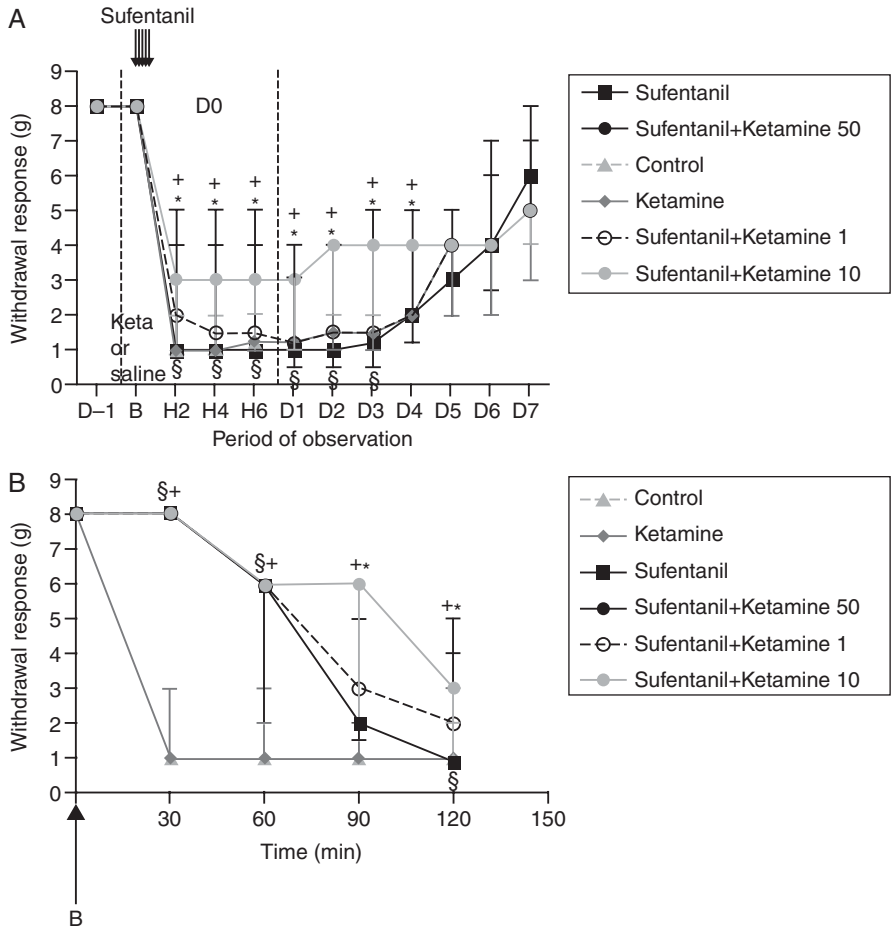

Fig 1 Effect of ketamine on the sufentanil enhancement of mechanical hyperalgesia (protocol A). No difference in the measured parameter was observed in any of the group after fracture and before treatment (A). At D0, sufentanil produced antinociceptive effects shortly after its administration (B). Sufentanil resulted in opioid-induced hyperalgesia from D0 to D3 (A). Sufentanil–ketamine association has produced antinociceptive effects shortly after its administration (B). Ketamine associated with sufentanil prevented opioid-induced hyperalgesia when compared with the sufentanil group; ketamine alone had no antinociceptive effect. The symbols represent median and inter-quartile range. $^{*}P<0.05$, the ketamine 50/sufentanil group *vs* the sufentanil group; $^{\S}P<0.05$, the sufentanil group *vs* the control group; $^{+}P<0.05$, the ketamine 1/sufentanil group *vs* the sufentanil group.

filament was pushed until it slightly bowed and then it was maintained in that position for 6 s. Each von Frey filament was applied once starting with 0.008 g and continuing until a withdrawal response was reached which was considered a positive response. The test was repeated three times. The lowest force from the three tests producing a response was considered the withdrawal threshold.

Thermal nociception

Thermal nociception was measured by a modified hot-plate test.[15] The time that a mouse would leave its hind paw on a hot plate at 52°C reflects thermal nociception (thermal latency). The paw was removed from the plate after a maximal time of 12 s by the investigator to avoid thermal injury and thermal hyperalgesia.[15] This test was repeated three times on each hind paw for each mouse.

Subjective pain scale

A subjective pain rating scale (0–5) modified from that described by Attal and colleagues[14] was used to quantify the pain, where: 0, normal; 1, curling of the toes; 2, eversion of the paw; 3, partial weight bearing; 4, non-weight bearing and guarding; and 5, avoidance of any contact with the hind limb.

Statistical analysis

On the basis of a previous study,[9] a power calculation for a 70% difference in the effect of morphine at postoperative D1 with a probability level of 0.05 and power of 0.80 ($1-\beta$) yielded a sample size of nine mice for each group. The values results of behavioural testing were not normally distributed and thus were analysed non-parametrically. To assess whether the withdrawal responses changed over time, Friedman's test was used. When Friedman's test was significant ($P<0.05$), pairwise comparisons were made using Wilcoxon's signed-rank test. Time point comparisons between the groups were first made using a non-parametric Kruskal–Wallis. When the Kruskal–Wallis test was

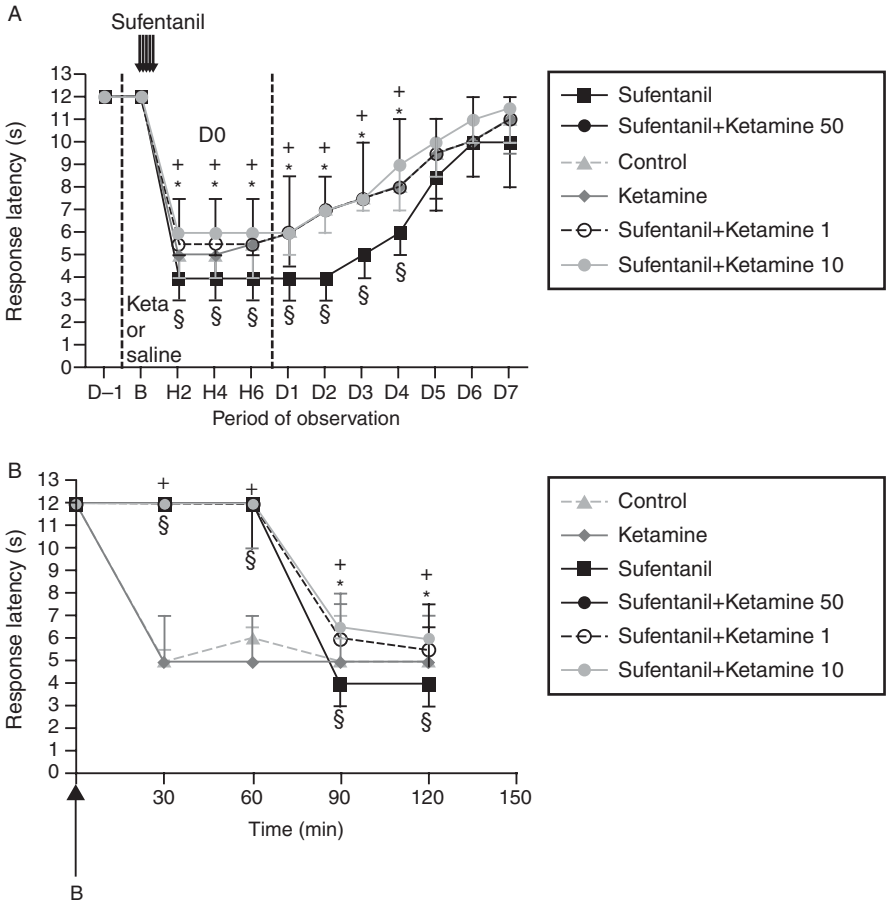

Fig 2 Effect of ketamine on the sufentanil enhancement of thermal hyperalgesia in (protocol A). No difference in the measured parameter was observed in any of the group after fracture and before treatment (A). At D0, sufentanil produced antinociceptive effects shortly after its administration (B). Then sufentanil has resulted in opioid-induced hyperalgesia from D0 to D4 (A). Sufentanil–ketamine association has produced antinociceptive effects shortly after its administration (B). Ketamine associated with sufentanil has prevented opioid-induced hyperalgesia when compared with the sufentanil group; ketamine alone had no antinociceptive effect. The symbols represent median and inter-quartile range. *$P<0.05$, the ketamine 50/sufentanil group *vs* the sufentanil group; $^{\S}P<0.05$, the sufentanil group *vs* the control group; $^{+}P<0.05$, the ketamine 1/sufentanil group *vs* the sufentanil group.

significant ($P<0.05$), pairwise comparisons were made using the Mann–Whitney *U*-test.

Results

Protocol A

Effects of ketamine on sufentanil enhancement of pain behaviour induced by fracture. Effects of ketamine pretreatment on the early analgesic effect of sufentanil (D0) and on the long-lasting effect of sufentanil (D1–D7).

No difference in the measured parameter was observed in any of the group before treatment (Figs 1A, 2A, and 3A).

At D0, sufentanil produced antinociceptive effects shortly after its administration with modification to mechanical and thermal stimulation (Figs 1B and 2B), and subjective pain scale (Fig. 3B). Sufentanil leads to development of opioid-induced hyperalgesia from D0 to D3 as shown by mechanical nociception (Fig. 1A) and from D0 to D4 as shown by thermal nociception (Fig. 2A). No changes were seen using the subjective pain scale after D0 (Fig. 3A).

At D0, sufentanil–ketamine association (1, 10, and 50 mg kg^{-1}) produced antinociceptive effects shortly after its administration with modification to mechanical and thermal stimulation (Figs 1B and 2B), and the subjective pain scale (Fig. 3B). Ketamine (1, 10, and 50 mg kg^{-1}) associated with sufentanil prevented opioid-induced hyperalgesia with modification of the response to mechanical nociception (Fig. 1A) and thermal nociception (Fig. 2A) when compared with the sufentanil only group. Ketamine alone had no antinociceptive effect when compared with the control group.

Protocol B

Effects of ketamine on postoperative morphine-induced analgesia.

No difference in any measured parameter was observed in any of the group after fracture and before treatment.

When administered 1 day after surgery in mice treated with sufentanil on D0, morphine induced an analgesic

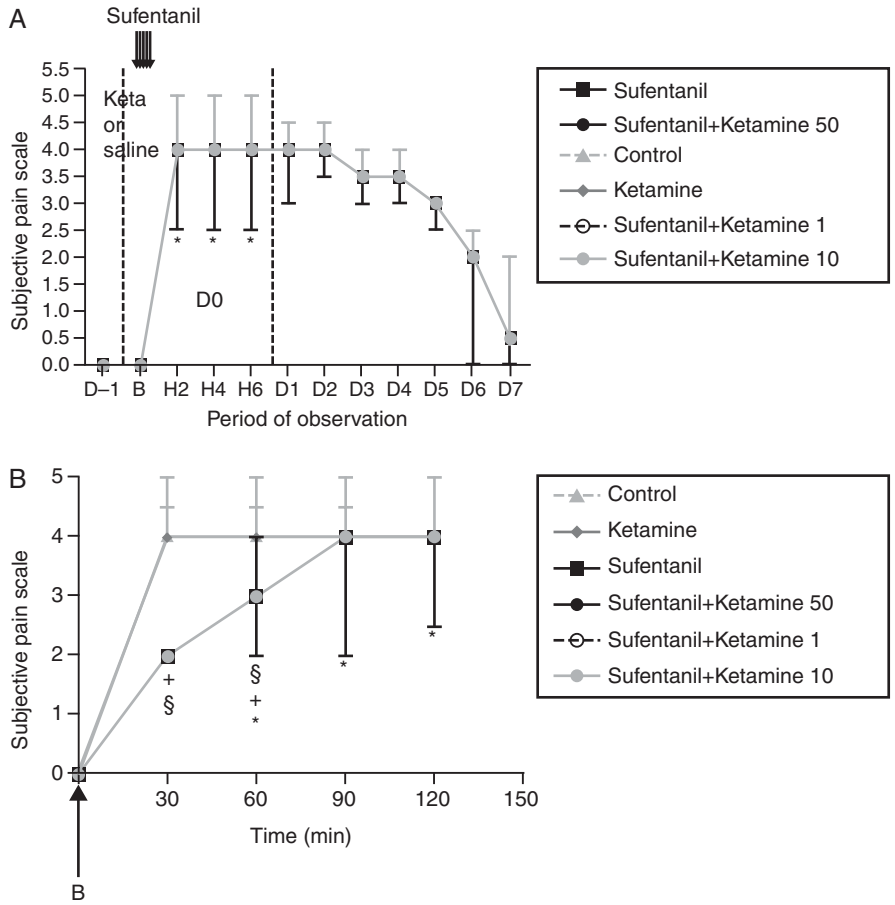

Fig 3 Effect of ketamine on the sufentanil enhancement of a subjective pain scale (protocol A). No difference in the measured parameter was observed in any of the group after fracture and before treatment (A). At D0, sufentanil produced antinociceptive effects shortly after its administration (B). No changes in the subjective pain scale were seen after D0 (A). Sufentanil–ketamine association has antinociceptive effects shortly after its administration (B). The symbols represent median and inter-quartile range. $*P<0.05$, the ketamine 50/sufentanil group *vs* the sufentanil group; $^{\S}P<0.05$, the sufentanil group *vs* the control group; $^{+}P<0.05$, the ketamine 1/sufentanil group *vs* the sufentanil group.

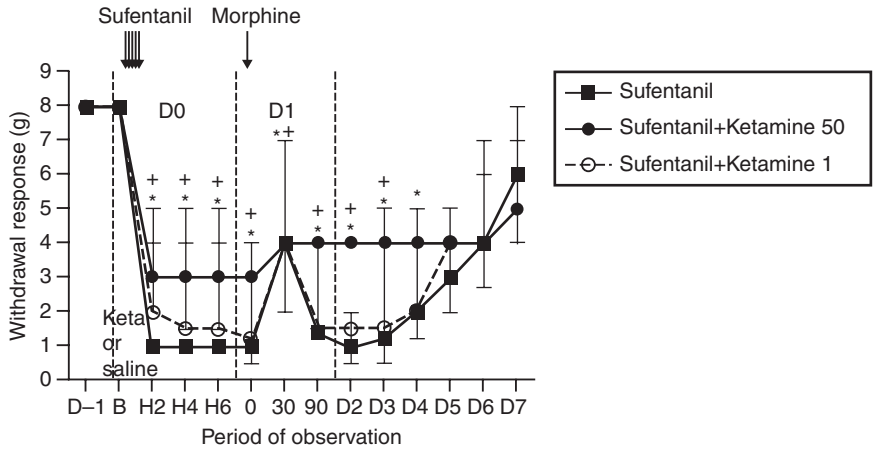

Fig 4 Effect of ketamine on the analgesic effect of a single morphine injection on mechanical hyperalgesia (protocol B). No difference in the measured parameter was observed in any of the group after fracture and before treatment. When administered 1 day after surgery in mice treated with sufentanil on D0, morphine induced an analgesic effect as observed by the nociceptive threshold increase in saline- and ketamine-treated mice. Morphine was more effective in ketamine-treated mice. The symbols represent median and inter-quartile range. $*P<0.05$, the ketamine 50/sufentanil group *vs* the sufentanil group; $^{+}P<0.05$, the ketamine 1/sufentanil group *vs* the sufentanil group.

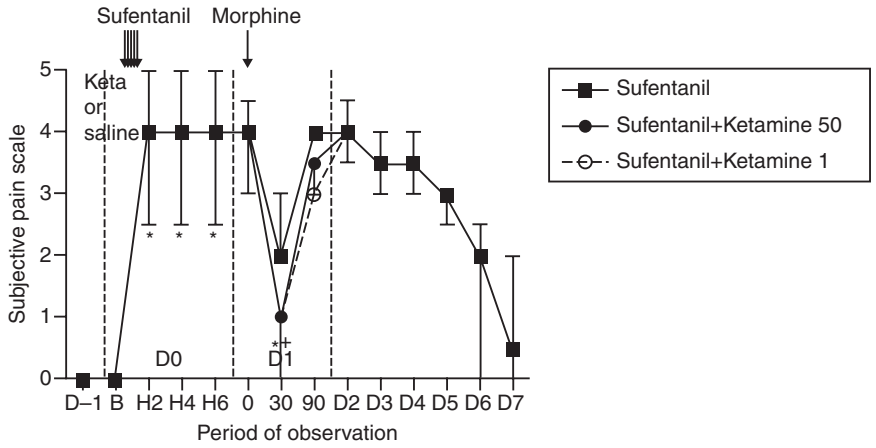

Fig 5 Effect of ketamine on the analgesic effect of a single morphine injection on a subjective pain (protocol B). No difference in the measured parameter was observed in any of the group after fracture and before treatment. When administered 1 day after surgery in mice treated with sufentanil on D0, morphine induced an analgesic effect as observed by the nociceptive threshold increase in saline- and ketamine-treated mice. Morphine was more effective in ketamine-treated mice. The symbols represent median and inter-quartile range. *$P<0.05$, the ketamine 50/sufentanil group *vs* the sufentanil group; $^{+}P<0.05$, the ketamine 1/sufentanil group *vs* the sufentanil group.

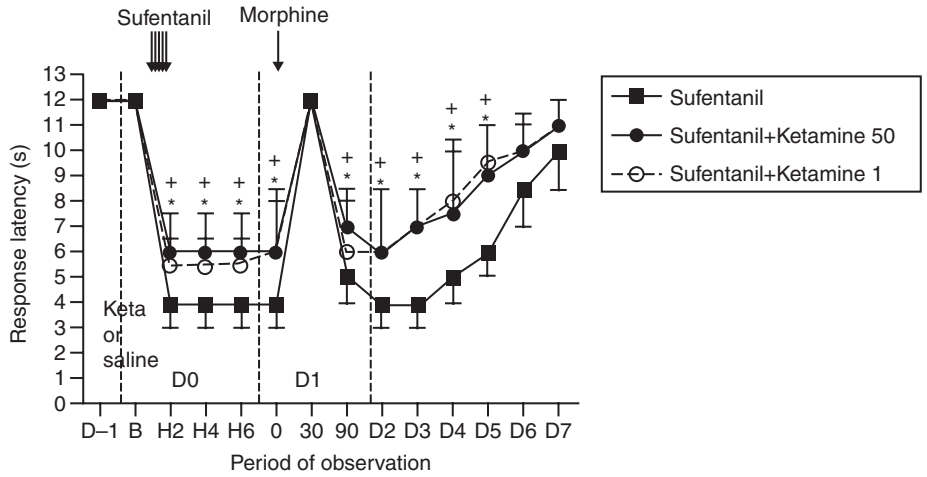

Fig 6 Effect of ketamine on the analgesic effect of a single morphine injection on thermal hyperalgesia (protocol B). No difference in the measured parameter was observed in any of the group after fracture and before treatment. No difference was found between the groups concerning thermal nociception after morphine administration probably because of the maximal threshold fixed at 12 s. The symbols represent median and inter-quartile range. *$P<0.05$, the ketamine 50/sufentanil group *vs* the sufentanil group; $^{+}P<0.05$, the ketamine 1/sufentanil group *vs* the sufentanil group.

effect as observed by the nociceptive threshold increase in saline- and ketamine-treated mice. Morphine was more effective in ketamine-treated (1 and 50 mg kg^{-1}) mice. Indeed, mechanical nociception and subjective pain scale were significantly modified in ketamine groups compared with the saline group (Figs 4 and 5), whereas no difference was found between the groups using thermal nociception where all groups reached the cut-off value, i.e. 12 s, after morphine injection (Fig. 6).

Discussion

In this study, we observed that ketamine reduced exaggerated postoperative pain and improved its management with morphine. Ketamine is often used in clinical practice to treat hyperalgesia.[12 16 17 18] Ketamine is a readily available, inexpensive drug that gives 30–50% reduction upon rescue analgesics.[12] It also provides decreased nausea and vomiting.[12] It appears efficient in a preclinical model of incisional pain,[8 9] but its effect in a post-fracture pain model in mice was still unknown. Balanced analgesia [*N*-methyl-D-aspartate (NMDA) receptor antagonist+ sufentanil] improves not only postoperative pain but also the effectiveness of morphine. Interestingly, even ketamine 1 mg kg^{-1} could produce antihyperalgesic effects. Moreover, there were small differences in the antihyperalgesic effects of ketamine between 1, 10, and 50 mg kg^{-1}. Thus, ketamine is a useful drug in terms of perioperative use of opioid, by diminishing opioid-induced hyperalgesia,

but also by improving morphine effectiveness. Rehabilitation and mobilization are important objectives in postoperative orthopaedic surgery to improve functional outcome and morbidity.[19 20] Multimodal analgesia allows a reduction in the doses of individual drugs for postoperative pain and thus a lower prevalence of opioid-related adverse events.[21] Our study confirms the finding of Richebe and colleagues,[9] where it was shown that exaggerated postoperative pain is not mainly associated with an excess of nociceptive inputs alone but also results from the development of hypersensitivity to nociceptive stimuli enhanced by perioperative opioid use.[6] Thus hyperalgesia and short-term tolerance induced by perioperative sufentanil use are closely related phenomena and may be prevented by the NMDA receptor antagonist ketamine.[9 22] Our results explain why most clinical studies previously reported that postoperative morphine consumption was decreased in patients who had received ketamine in association with opioid for surgery.[23 24]

Ketamine does not prevent hyperalgesia in all types of pain; for example, preoperative low-dose administration of i.v. ketamine did not result in a clinically meaningful reduction in pain or morphine consumption in men undergoing radical prostatectomy under general anaesthesia.[25]

We recently described a post-fracture pain model in mice which imitates post-fracture pain.[3] However, in the present study, the model closely mimics an orthopaedic procedure, and the fracture occurred during sufentanil administration, that is, under general anaesthesia (sedation+analgesia). We found that ketamine diminishes short-term hyperalgesia (at D0) produced by sufentanil administration for all behavioural testing, and also diminishes long-term hyperalgesia for thermal and mechanical nociception. Attempting to offer pre-emptive antihyperalgesia could be a fascinating challenge for modern anaesthesiology because chronic pain occurs in 10–50% of patients after surgery.[2 26] Indeed, the paradoxical phenomenon of opioid-induced hyperalgesia has been described to develop rapidly after a single opioid exposure in animals, human volunteers, and surgical patients.[27] Early administration of antihyperalgesic agents such as ketamine might be useful strategies for improving pre-emptive analgesia.[9 28 29] Although the non-competitive NMDA receptor antagonist ketamine acts on a variety of receptors,[30] we selected it because it has the advantage of being easily available to anaesthetists.[9] Interestingly, ketamine also improves morphine action on postoperative pain management. We found a pain diminution in terms of both mechanical and subjective pain scale, signifying better mobilization. We found no difference in thermal stimulation, probably because we used a maximal time of 12 s to avoid thermal injury and thermal hyperalgesia.[15] As morphine is effective in post-fracture pain management,[3 4] the maximal time of 12 s was reached in both groups (ketamine and saline).

In conclusion, our results suggest that pre-emptive use of ketamine is useful in orthopaedic surgery to diminish short- and long-term hyperalgesia, but also to improve morphine effectiveness leading to a better mobilization and more rapid rehabilitation.

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