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Subanaesthetic ketamine spares postoperative morphine and controls pain better than standard morphine does alone in orthopaedic-oncological patients

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ABSTRACT

Background: Postoperative pain in patients with bone and soft tissue cancer is different from that of other surgical patients due to the severity of the pain generated during surgery and because many of them have already been in pain preoperatively. The search for optimal intravenous pharmacologic management for this population is an ongoing one. We conducted a 10-month prospective, randomised, double blind study to compare the effects of a standard morphine dose to a 35%-lower dose plus a subanaesthetic dose of ketamine for postoperative pain control in patients undergoing bone and soft tissue cancer surgery under standardised general anaesthesia.

Methods: After extubation, when objectively awake (⩾5/10 on a 0–10 visual analogue scale (VAS)) and complaining of pain (⩾5/10 VAS), patients were connected to an intravenous patient-controlled analgesia (IV-PCA) device that delivered 1.5 mg morphine/bolus (MO group) or 1 mg morphine + 5mg ketamine/bolus (MK group), with a 7 min lockout time. Rescue intramuscular diclofenac 75 mg was available Q4/day. Follow-up lasted 96 h.

Results: Fifty-seven patients (24 males, aged 18–74 years) completed the study. Pain scores were lower in the MK group compared to the MO patients, although MO patients ($n = 29$) used 32.9 ± 24.9 mg/patient morphine during the first 24 postoperative h compared to 14.6 ± 11.4 mg/patient ($P < 0.05$) for the MK patients ($n = 28$). At that time point, 11 MO versus 4 MK patients still required IV-PCA ($P < 0.05$). Diclofenac was also used more in the MO group. All vital signs were similar between the groups. The physiotherapy score was 35% higher for the MK patients ($P < 0.05$). No patient had hallucinations. Postoperative nausea and vomiting rates were higher in the MO group.

Conclusions: The use of subanaesthetic ketamine plus 2/3 the standard dose of morphine following bone and tissue resections results in 1) lower and more stable pain score, 2) ~60% morphine sparing effect, 3) a shorter period of postoperative IV-PCA dependence. Such therapy is also associated with better early physical performance.

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1. Introduction

1.1. Nociception

The pharmacological management of postoperative pain in patients with bone and soft tissue cancer is problematic due to the severe pain generated during surgery and because many are already in pain preoperatively.[1] Intravenous (IV) protocols employ various regimens of opioids and their congeners which are often only of partial benefit.[1] The self-administered patient-controlled analgesia (PCA) technique aims at controlling pain at the lowest effective IV dose with the patient being involved in determining the analgesic amounts needed. This technique adjusts levels of pain control better than IV boluses and also increases patient satisfaction and cooperation, while respiration and haemodynamic parameters remain unaffected.

1.2. Analgesics

The role of the N-methyl-D-aspartate receptor (NMDAR) in modulating acute pain and the subsequent central sensitisation has been discussed before.[2–4] NMDAR antagonists reduce pain perception without depressing haemodynamic parameters or respiration, thereby avoiding opioid-associated hazardous consequences. This consideration is most pertinent to patients who undergo prolonged surgery and/or large musculoskeletal tumour resections and where full orientation and collaboration are important postoperatively. NMDAR inhibition, particularly pre-incisionally,[5,6] also preempts the arousal of the spinal cord and inhibits the wind-up process, thus reducing central perception of pain. Both dextromethorphan and ketamine are non-competitive NMDAR antagonists. Dextromethorphan has a low rate of side effects, a long history of clinical safety[7] and can preempt analgesia.[8] We have previously demonstrated that preoperative oral dextromethorphan reduces short- (6 h) and long-term (up to 3 days) self-administered morphine and diclofenac requirements following surgery under either epidural or general anaesthesia.[9,10] We then documented the beneficial effects of dextromethorphan in orthopaedic-oncological patients who had undergone surgery under general anaesthesia for bone and soft tissue malignancies and who later made use of morphine IV-PCA.[11] Currently, dextromethorphan can only be used orally in the clinical setting.

1.3. Ketamine use for pain and aims of study

Ketamine enhances opiate-induced acute and chronic antinociception.[12] It reduces hyperalgesia and prevents opioid tolerance in animals[13] and morphine resistance in humans.[4,14] The concomitant administration of ketamine and morphine also lowers morphine consumption, both in the immediate and delayed postoperative period.[15,16] Given that subanaesthetic (⩽500 μg/kg) doses of ketamine alone rarely produce undesirable haemodynamic alterations (e.g. elevated heart rate and blood pressure)[17] or dissociative effects, we demonstrated that by combining such a dose of ketamine with morphine, we could both effectively control pain and reduce the amount of morphine consumption in general surgery patients.[16] Once this was proven, we aimed at putting together the same IV-PCA technique, combining it with the knowledge and safety of ketamine in general surgery with that of the usefulness of dextromethorphan in orthopaedic-oncological patients who undergo bone and soft tissue sarcoma resection under general anaesthesia.[10]

2. Patients and methods

2.1. Patient selection

Patients of American Society of Anaesthesiologists (ASA) physical status I–III who were scheduled for one of the two major bone and soft tissue tumour surgeries (see below) under standardised general anaesthesia between January–October 2005 were enrolled in this prospective, randomised, double blind study. The protocol had been approved by our institutional human research and ethics committee. All orthopaedic-oncological patients scheduled for surgery, without exception, experience preoperative cancer-associated pain that is, however, satisfactorily controlled (VAS ⩽4/10) by non-steroidal anti-inflammatory drugs (NSAIDs), or oral opioids.

During the preoperative visit, the anaesthesiologist gave each patient a full explanation of the rationale for the study, the PCA device and the mode of self-administration of the contained drug(s), and directions on how to use the linear visual analogue scale (VAS) for pain and during other subjective evaluations .The patient then gave a written consent to participate in this study.

2.2. Surgery cases

Surgery consisted of one of the following procedures[11] in any part of the body:

Type 1: resection of a single muscle or a single muscle group with no reconstruction, bone tumours treated by local curettage with no segmental resection, soft tissue tumour of ⩽8 cm diameter with minimal bone involvement. This surgery took up to 3 h to accomplish and/or necessitated ⩽3 units of blood;

Type 2: large-sized soft tissue resections necessitating tissue transfer and reconstruction, forequarter amputation, large bone resection and reconstruction, hemipelvectomy. These procedures involved large bone tumours with or without soft tissue tumours of >8 cm diameter. Such surgery lasted <6 h and/or necessitated <6 units of blood.

The same surgical and anaesthesia teams performed all the procedures, which provided the data for this study.

Patients were evaluated by a ward nurse at their arrival to the hospital; their self-rated level of pain by VAS and their analgesics regimens were recorded. Pain above 4/10 VAS caused the exclusion of the patient from the study. Other exclusion criteria were allergy to morphine, ketamine, NSAIDs or any of the intraoperative drugs. The use of opioids by any route, sedatives or centrally acting drugs (e.g. CNS depressants or antidepressants) during 21 days prior to surgery, or the preoperative application of central neuroaxial blocks caused exclusion as well. Also excluded were patients

younger than 18 years of age, pregnant women and individuals suffering from congenital or acquired neuromuscular disease or chronic pain (unrelated to the current disease), cardiac, liver or renal dysfunction (based on patient's history, physician's report and community-prepared analyses), those with past or current neuropathy or psychological disturbances, as well as those who used centrally active psychomimetic drugs, or showed evidence of sepsis or infection up to 1 week prior to randomisation.

2.3. Randomisation

Study quality was assessed using the Jadad criteria: random allocation of treatments with a clear description of randomisation procedure; blinding of the patient for the assigned treatment; blinding of the outcome assessor; and description of dropouts and missing values.[18] Randomisation was assigned to patients of the two groups according to their national ID number. When the PCA device was to be connected to the patient and started, an unbiased anaesthesiologist prepared the syringe based on the randomisation list. The allocation sequence was generated and concealed at the computer of that colleague and the blinding was maintained by using an identification number of the randomisation list and assigning it to the drug-containing syringe of each participating individual. In addition, patients who withdrew, dropped-out, or were lost to follow-up, were incorporated in the analyses by the 'intention-to-treat' analyses of the baseline data; their outcomes, if any, were neither assessed nor interpreted in the data body.

2.4. Anesthesia and surgery protocols

All patients were given standardised balanced general anaesthesia; no regional block was used. Anaesthesia was induced with IV injection of midazolam (2 mg), propofol (1–1.5 mg/kg), fentanyl (3–5 μg/kg) and atracurium (0.1 mg/kg) to facilitate endotracheal intubation and for later maintenance. All patients were ventilated using volume-preset time-cycled anaesthesia ventilators with N_2O/O_2 (6 ml/kg tidal volume) enriched with isoflurane (0.4–0.8% expired concentration) and as deemed necessary by the attending anaesthesiologist. At the end of surgery, the patients' neuromuscular relaxation was reversed pharmacologically and they were extubated in the OR. The patients were taken to the post-anaesthesia care unit (PACU) for immediate postoperative follow-up.

Intra- and postoperative fluids and blood replacement were based on haemodynamic indices, blood loss, haemoglobin levels and the amount of urine collected via an indwelling urinary catheter. Perioperative monitoring included a 5-lead electrocardiograph, systolic and diastolic blood pressures, core temperature (monitored intraoperatively only), respiratory rate, $EtCO_2$ (where available) and fingertip pulse oximetry (SpO_2), using the AS/3™, Datex-Ohmeda® monitor, Helsinki, Finland. Arterial and central venous lines were placed at the anaesthesiologist's discretion.

2.5. Pain control administration and assessment

The PACU attending physician started the IV-PCA device in all patients when sufficiently awake (⩾5/10 VAS: only this initial measurement of wakefulness was objective, with all later measurements being self-rated by the patients). Analgesia was started when a patient rated his/her pain ⩾5 on a 0–10 VAS (see below).[16] A cutoff pain score of 5 was chosen on the basis of previous experience in acute pain control.[2,6,11,16] Drug injections consisted of a solution that contained 1.5 mg morphine (group MO) or 1 mg morphine plus 5 mg ketamine/bolus (group MK). The attending physician administered the first dose, after which the IV-PCA device was activated. The device was preset to deliver a bolus whenever the patient activated it, controlled, however, by a 7 min lockout period. If pain was not attenuated within 30 min of treatment, a rescue dose of intramuscular diclofenac 75 mg was available as for Q4/day. Any additional requirement of analgesics led to the exclusion of the patient from the study. Patients could make use of the PCA for a maximum of 96 h.

The patients remained in the PACU for 3 h in order to assure the recognition of possible late onset of pain or sedation. They were then transferred to the orthopaedic-oncological department in accordance with the study protocol and the PACU discharge regulations.

The blinded nurses, both in the PACU and the ward, recorded the levels of pain and wakefulness as well as haemodynamic and respiratory data for each patient every 15 min for the first 2 h, every 30 min for the next 2 h and Q6 h until the IV-PCA device was disconnected. The indication to discontinue it was either that the patient did not make use of it for 8 h or if 96 h had elapsed since it was started. The following parameters were assessed (VAS was assessed using the 100 mm chiroscience pain gauge):

1. Subjective pain intensity using a VAS from 0 (no pain) to 10 (unbearable pain)
2. Subjective sedation based on a VAS from 1 (fully awake) to 10 (heavily sedated)
3. Hourly analgesia consumption
4. The rate of PCA activation, considered as being the number of times the delivery button was pressed
5. Physiotherapist's blinded evaluation was done on patients who underwent lower limb surgery. It was based on day 1 (after surgery or when allowed to move out of bed) independent getting off bed, and on day 3 going up and down ten stairs without help.

Since significant changes in vital signs might affect cognition or pain sensation, a >20% variation from the values that had been recorded during the premedication visit throughout the study, or a $SpO_2 < 92\%$ under 40% oxygen at any time, excluded the patient's data at that time point. Data of patients unable to cooperate at a given time point was excluded at those intervals.

Untoward effects (e. g. nausea, vomiting or any distress) were recorded by the nurse and treated as indicated (e. g. metoclopramide 10 mg IV for nausea or vomiting).

2.6. Statistical analysis

The statistical analyses were performed at the Statistical Laboratory of the School of Mathematics, Tel Aviv University, using the SPSS Release for Windows, Version 12.01 (USA,

2003). A power analysis had been done in advance to answer the primary question, i.e. what was the effect of ketamine on PCA consumption in the patients undergoing orthopaedic-oncological surgery. In order to obtain a power of 0.90 where delta (difference in morphine consumption/patient) = 2.5 during the first postoperative 30–60 min and alpha = 0.05, each study group required an enrollment of 16 patients or more. Demographic data and vital signs (premedication and baseline heart rate, systolic and diastolic blood pressures, respiratory rate, SpO_2, mean amounts of fentanyl used intraoperatively, and duration of surgery) of the two study groups were compared using the one-way analysis of variance (ANOVA) with repeated measures. Gender and ASA physical status were analysed using the Pearson χ^2 test. ANOVA was also used to evaluate the physiotherapist's individual evaluations. The rates of hourly demands for IV-PCA adminis-

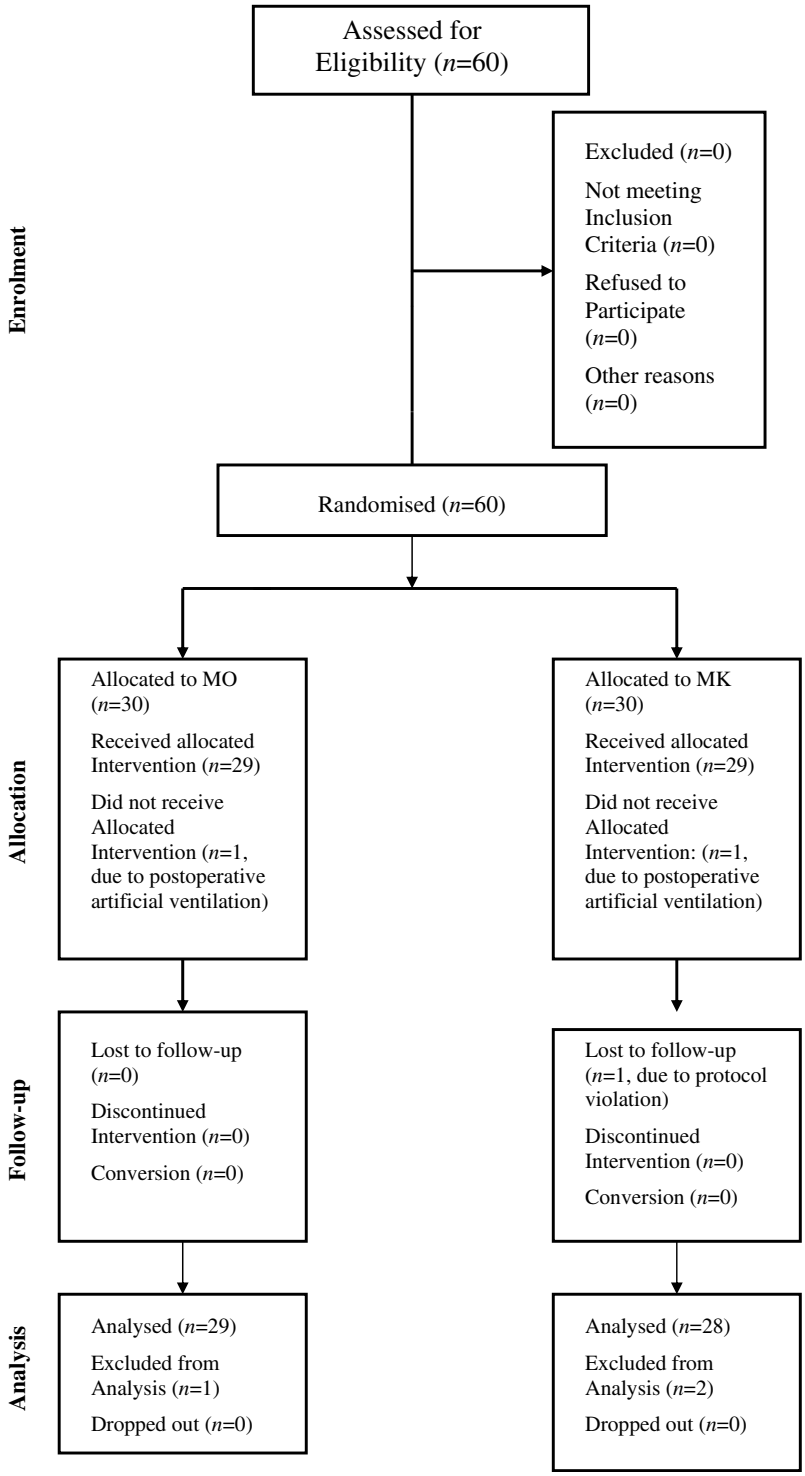

Fig. 1 – Flow diagram of the progress through the phases of the randomised trial. MO, morphine only-administered group; MK, combined morphine + ketamine-administered group.

tration and its actual use were square-rooted in order to obtain their normal distribution; the results were then analysed by one-way ANOVA with repeated measures. The number of times the patients received a rescue drug, anti-emetics, or those who were dependent on urinary catheter more than 24 h after surgery, and the rate of side effects, were analysed using the Fisher Exact test. The effects of type of analgesia on the patients' self-rated pain and grade of wakefulness (VASs) were also analysed using the AN(C)OVA with repeated measures; their means were then compared using the Student's *t*-test. The ANOVA tests were always followed by the post-hoc Tukey's Honest Significant Difference method. The background data of patients who dropped out of the study were analysed following the intent-to-analyse format. All values are expressed as mean ± standard deviation (SD) or absolute numbers, with significance defined as $P < 0.05$.

3. Results

3.1. Consort description

Sixty patients fulfilled the study criteria for randomisation. One MO and two MK patients dropped out of the study (see CONSORT Statement, Fig. 1). The demographic, anaesthesia and surgical data were similar between the two study groups, as were those for pre-surgery pain VAS ranges and analgesics (Table 1), intra-operative blood replacement and fluid infusion (data not shown). Baseline (immediately before starting IV-PCA) vital signs, and PACU coherence, pain intensity and wakefulness initial scores were also similar between the groups.

3.2. Analgesics use

Overall, the amount of analgesics requested by the patients was drug-regimen associated. The MK group used ~40% the amount of morphine used by the MO group during the 96 h of study, and half the doses of diclofenac ($P < 0.05$) (Table 2). The latter patients also activated the PCA device three times the hourly usage registered among the former group during the first 24 postoperative h ($P = 0.02$) (Table 2). This trend lasted for 32 h postoperatively (data not shown). Furthermore, the decay curve of the number of patients still using their IV-PCA demonstrated that MK patients were off sooner than MO patients. At 24 h, 11 MO patients still required IV-PCA compared to four MK individuals ($P < 0.05$) and four versus zero patients, respectively, at 32 h. At 96 h the usage of morphine in the MO group was >2-fold that used by the mixed-drug group (Table 2).

3.3. Pain assessment

Pain intensity was also drug-dependent: there was a time*-drug group statistical interaction ($P < 0.001$). While pain VAS demonstrated an overall decline throughout the study period, the MO group was characterised by higher scores, sometimes associated with irregular peaks over that time. In contrast, the MK group had significantly lower VAS scores; this level of reduced pain intensity remained stable throughout the 96 postoperative h (Fig. 2). This was despite the larger amounts of morphine administered to the former group (see above). Importantly, the subjectively rated level of wakefulness was also consistently better for the MK compared to the MO group, especially during the 2nd POD ($P < 0.001$) (Fig. 3).

3.4. Vital signs

Systolic and diastolic blood pressures, and respiratory rate, were similar between the groups. Contrarily, heart rate in the MK patients was significantly ($P = 0.0065$) lower that that in the MO group (data not shown). None of the MK patients had $SpO_2 < 94\%$ under 40% oxygen facemask compared to two MO patients. No data were excluded from analyses due to changes <20% of baseline cardiovascular values.

Table 1 – Demographic, anaesthesia and surgery data, and baseline vital signs[a] (absolute numbers, mean ± SD)

	Morphine only (MO) ($n = 30$)	Morphine + ketamine (MK) ($n = 30$)	*P* Value
Age (years)	40 ± 16	43 ± 17	0.48
Weight (kg)	69 ± 11	70 ± 17	0.79
Gender (male/female)	16/14	11/19	0.09
ASA (class, 1/2/3)[b]	15/10/5	11/15/4	0.1
Pain VAS at admission	2.6 ± 1.0	2.7 ± 1.0	0.7
Patients using pre-operative paracetamol/NSAIDs/none	21/12/3*	19/16/4[a]	0.14
Intraoperative fentanyl (μg/patient)	274 ± 101	246 ± 129	0.35
Surgery time (min)	117 ± 48	113 ± 58	0.77
Surgery Type 1/2	15/15	13/17	0.18
Baseline vital sign			
Heart rate (beats/min)	81 ± 13	76 ± 11	0.11
Respiratory rate (breaths/min)	14 ± 5	13 ± 7	0.53
Systolic blood pressure (mm Hg)	130 ± 17	131 ± 17	0.82
Diastolic blood pressure (mm Hg)	72 ± 16	73 ± 9	0.77
Pulse oximetry (SpO_2, %)	97 ± 2	98 ± 2	0.06

Abbreviations: ASA = American Society of Anaesthesiologists physical class; VAS = visual analogue scale.
a Including data of the three dropouts (intent-to-treat analyses).
b Number of patients in the various ASA functional classes.

Table 2 – Postoperative effects of test drug treatments (mean ± SD or absolute numbers)

	Morphine only (MO) (*n* = 29)	Morphine + ketamine (MK) (*n* = 28)
24h IV-PCA overall activation (*n*/h/patients)	14.9 ± 6.7	5.8 ± 2.7*
25–32h IV-PCA overall activation (*n*/h/patients)	1.9 ± 1.7	0.7 ± 0.6**
24h morphine use (mg/patients)	32.9 ± 24.9	14.6 ± 11.4***
96h morphine use (mg/patient)	38.0 ± 35.7	18.8 ± 20.67*
Use of diclofenac (*n*, d1/d2/d3)	9/6/2	5/2/1**
PONV (*n*, d1/d2/d3)	7/5/0	4/1/0****
Urinary need for catheterization >24h (*n*)	16	10*
1–3 POD physical therapist 0–10 score (*n* = 14/group)	6.4 ± 1.4	8.8 ± 1.4*****

*P = 0.02, **P = 0.01, ***P < 0.05, ****P = 0.03, *****P = 0.0001 versus the morphine-only group.
Abbreviations: *n* = number of patients; MO = morphine only-administered group; MK = morphine + ketamine-administered group; d = day; PONV = postoperative nausea and /or vomiting; POD = postoperative day; VAS = visual analogue scale.

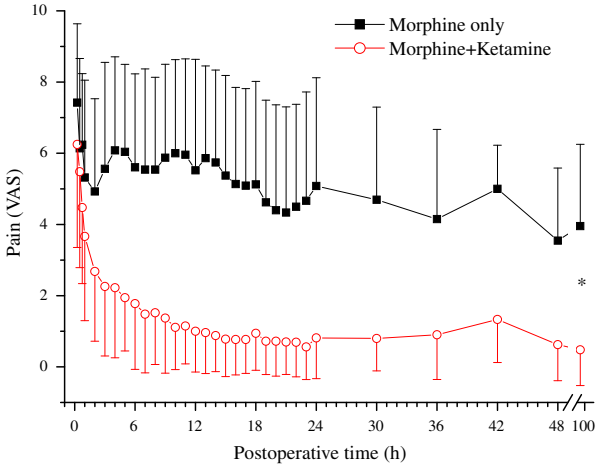

Fig. 2 – Postoperative patients-self-rated pain by visual analogue scale (VAS). *P < 0.001 (by ANOVA with repeated measures) between the groups.

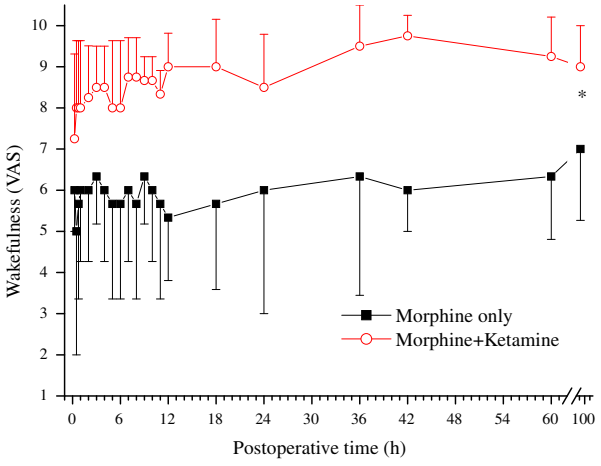

Fig. 3 – Postoperative patients-self-rated level of wakefulness (visual analogue scale, VAS). *P < 0.001 (by ANCOVA with repeated measures) between the groups.

A lower rate of urinary catheter dependence was observed in the MK group >24 h ($P < 0.05$) (Table 2). The physiotherapist's judgment of patients' physical performances during the first 3 postoperative days showed better scores for the MK group than for the MO group ($P < 0.05$) (Table 2).

3.5. *Side effects*

The MO patients' rate of nausea and vomiting (PONV) was higher than that of the MK patients ($P < 0.05$) (Table 2); all incidents were short-lived and responded well to metoclopramide. No ketamine-specific side effects were recorded; no patient of either group returned to the operating room for re-surgery.

4. Discussion

This is a prospective, parallel randomised, double blind trial of postoperative analgesia where standard IV-PCA-MO dose was compared to a mixture of 66% the MO plus a subanaesthetic ketamine dose. The main value of this study lies in the result that the latter protocol controlled pain and spared morphine two-fold compared to the standard MO usage, and at the same time was safe and provided both stable vital parameters and physical therapists' evaluation in this problematic and painful population.

4.1. *Importance of effective postoperative pain*

Postoperative pain is one of the major fears of patients following surgery, especially among those undergoing procedures for bone and tissue cancer. Pain prevails over almost all other symptoms in these cancer patients. In case of uncontrolled pain, post-operative complications may occur more frequently and severely, and discharge from hospital is often delayed.

Optimal management of post-operative pain, therefore, is very important. Studies aiming at improving pain management in orthopaedic-oncological patients are scarce. This study suggests a new medical strategy, the combination of subanaesthetic dose of ketamine and reduced morphine dose, which is studied versus standard morphine alone. The study offers a new treatment option in the management of post-operative bone cancer pain, showing that all parameters in the former group of patients were better than in the latter, especially pain score and level of satisfaction.

We have previously shown the usefulness of NMDAR inhibitors on lowering morphine consumption after general

surgery.[16] The safety profile of the present drug combination has been discussed previously,[4,16] however, not in the current patient population. The present protocol took these data one-step forward from two aspects: the nature of the cohort (where preoperative pain is the norm) and the use of only 2/3 the standard morphine dose.

4.2. *Ketamine mode of antinociceptive activity*

The mechanisms by which ketamine potentiates antinociception have been widely discussed before.[4,19] Briefly, ketamine at low doses produces antinociception through its high affinity to the NMDAR, antagonising its activity.[13] While morphine and other opioids produce antinociception through activation of the mu receptor and the monoaminergic descending pathways at the spinal level,[20] they also activate the NMDAR, resulting in central sensitisation of pain, induction of hyperalgesia and the development of tolerance to opioids.[20,21] Tolerance is one of the mechanisms of severe postoperative pain, which lead to the need for high doses of opioids in postoperative patients. Small doses of ketamine act specifically to prevent such tolerance and pain sensitisation.[22] We had documented the usefulness of a similar pharmacological combination after a combined general and epidural anaesthesia for orthopaedic-oncological patients[23] as well, but not all patients are suitable for a combined anaesthesia protocol consisting of general and regional anaesthesia. The present study describes a methodology of providing an analgesic protocol even after general anaesthesia, and it emerged as being suitable for these patients.

If given alone, ketamine in minimal doses ($\leqslant$250 μg/kg IV) induces a short-lasting sedation, correlating with the brief high peak plasma concentration that develops immediately after the injection.[24] Whereas the plasma half-life of ketamine is only 15–20 min, the analgesic effect of the morphine-ketamine combination was evident throughout the 96 h observation period, even though we did not deliver IV-PCA after an interval of 72 h post surgery.

4.3. *Clinical aspects of effective pain control*

Besides the importance of outlining a new and advanced antinociceptive pain protocol for these patients' well being, it apparently did not achieve economic endpoints of better final outcomes, such as reduced hospital stay or costs, but did provide better functional scores. Our earlier works showed higher satisfaction rate, but no statistical difference between similar groups of patients with regard to first ambulation and home discharge, although the combined regimen-treated patients had better outcomes than the morphine-treated ones.[11] This is mainly because of the particularity of this cohort which needs a long hospital stay before being discharged Nevertheless, patients' enhanced abilities to perform designated exercises after complex resectional and prosthetic interventions strengthen the case for administering ketamine in oncological-orthopaedic patients, both for better pain control and for a superior rehabilitation process. We are currently investigating the potential long-term rehabilitation benefit of the MK drug protocol.

Respiratory rate, oxygenation and adequate ventilation may drastically worsen if sedation is too deep, such as that caused by large doses of narcotics given within a short period of time to alleviate severe pain.[25,26] We had observed such occurrences in similar MO groups[11]: 23% of such patients required the administration of high concentrations of inspired oxygen to compensate for low minute ventilation. On the other hand, MK patients, both in an earlier study[16] as well as in the present one, exhibited improved oxygen saturation levels soon after starting postoperative antinociceptive therapy, probably because their enhanced pain control improved their ability to breathe deeply and cough effectively, and, most importantly, this combination allowed for a substantial reduction in the cumulative amount of morphine consumption. Ketamine also sustains the patency of small and large airways, thus preventing them from obstruction, such as the kind that could occur in patients under the effect of excessive opioids.

4.4. *Ketamine and untoward effects*

Although ketamine is known to increase heart rate and blood pressure due to its pro-adrenergic effect, our MK patients did not demonstrate these reactions, either because of the low ketamine dose per bolus and/or because of its combination with morphine. The current demonstration of lower heart rate could result from the better pain control in the MK patients, indicative of the haemodynamic safety of ketamine in orthopaedic-oncology, similar to that in general surgery patients.[4]

Historically, the administration of ketamine alone has been linked to several untoward effects, one of which is drowsiness.[27,28] Our MK patients, however, self-rated themselves more awake than their MO counterparts, supporting the findings of our earlier reports.[4,16] Short-lived hallucinations are, however, the most frequently mentioned side effect of ketamine, especially if administered at doses $\geqslant$500 μg/kg.[29,30] Some reports have indicated that up to 30% of the patients receiving IV anaesthesia doses of ketamine (0.5–1.5 mg/kg) experience unpleasant dreams or acute psychosis-like symptoms.[31] Again, in our present MK group, there were no reports of illusions or bad dreams, a finding we consider an index of safety, which is likely due to the small and intermittent dosing of the drug.[4,16] This drug combination appears to be particularly efficacious and safe for patients with severe orthopaedic-oncology involvements, which are characteristically associated with the perioperative use of large dosages of analgesics because of their lower threshold of pain, especially those individuals with a history of radio- or chemotherapy and other debilitating procedures that are known to induce pain, nausea and vomiting.[1,32]

4.5. *Limitations*

This study is a controlled study powered on low morphine consumption in the first 30–60 min post-operatively. Although it has not been powered to detect clinical improvement in pain control during the first three post-operative days, we did find significant differences in perceived pain in the MK patients later on in the recovery period. This is because the cohort herein recruited is almost double the minimal power stated initially. A larger, adequately powered, study is

warranted in order to conclude that ketamine indeed improves pain control and revalidation when combined with a lower than usual dose of morphine.

4.6. *Conclusions*

The addition of a minimal dose of ketamine to only 66% of the standard dose of morphine provides better immediate and prolonged pain relief than that obtained by the standard dose of morphine alone in patients undergoing bone and soft tissue tumor resection. This was achieved despite the ~60% lower amounts of morphine used by these patients. The MK patients' haemodynamic and respiratory profiles were stable and their levels of wakefulness superior compared to the MO patients. The MK patients had superior scores in their physical performances and, not surprisingly, side effects were negligible and brief, further supporting our conviction that the described protocol is safe and useful for patients undergoing orthopaedic-oncological procedures.

Conflict of interest statement

None declared.

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