Morphine sparing effect of low dose ketamine during patient controlled analgesia

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KEY WORDS: Ketamine, morphine sparing effect, patient controlled intravenous analgesia.

Abstract
Objective: To compare the quality of intravenous patient controlled analgesia (PCIA) of low dose morphine plus ketamine with morphine. Design: Double blind case control study. Setting: Academic hospital. Patients: Thirty-six patients scheduled for elective abdominal hysterectomy were randomly divided into two groups to receive patient controlled intravenous analgesia (PCIA). Interventions: Group M received morphine 21 µg/kg as a bolus, Group MK received morphine 7 µg/kg plus ketamine 14 µg/kg as a bolus. The lockout period in both groups was 7 minutes. Measurements: Morphine consumption, visual analogue pain score (VAPS), pulse oximetry oxygen saturation (SpO₂), respiratory rate (RR), verbal descriptive sedation score (VDSS), nausea, pruritis, dreaming, and hallucinations were recorded at 1, 4, 24 and 48 hours. Equivalence of the two groups was assessed by comparing the 95% confidence interval (CI) for the effect with the equivalence delta (10%). Results: Morphine consumption was significantly lower in Group MK after 24 and after 48 hours (p < 0.05). VAPS was significantly higher in Group MK at 4 hours (p < 0.05), but VAPS was always clinically lower than in Group MK at all times (Equivalence delta > 10%). SpO₂ at 4 hours was marginally higher in Group MK (p = 0.0809). Conclusion: Morphine-ketamine PCIA, in doses used in this study, provided analgesia inferior to that of morphine PCIA, but may improve the respiratory side effect profile of morphine. The analgesia of morphine and ketamine are additive rather than synergistic.

Morphine remains the gold standard for analgesia against which the effectiveness of newer drugs and combinations are measured. It has been the standard analgesic for many years, and the effects of newer analgesics are often expressed in terms of the effect of morphine. The search for good analgesics should not only focus on analgesia. As far as analgesia is concerned, morphine is an excellent drug, but morphine lacks quality of analgesia due to its side effects. These side effects include sedation, respiratory suppression, nausea and vomiting, and pruritus. These side effects may be avoided or reduced by the co-administration of other analgesics, e.g. ketamine.

Apart from postoperative analgesia, ketamine has found application in other fields of analgesia. An oral ketamine suspension has been found superior to a paracetamol-codeine-diphenhydramine suspension as analgesic and sedative for wound care procedures in children.¹ Oral ketamine may also have potential in the treatment of neuropathic pain, including stump pain.² The effect of co-administered drugs depends on pharmacodynamic (agonism or antagonism) and pharmacokinetic interactions. When drugs with the same end point (analgesia) affect different receptors, they may be synergistic. C and Aδ fibres conduct nociceptive stimuli to the cell bodies in dorsal ganglia. Axons from these cells release glutamate, aspartate, and substance P. These neurotransmitters stimulate N-methyl-D-aspartate (NMDA) receptors on the cell bodies in the dorsal horn and gives rise to delayed, prolonged and increased pain (spinal wind up).³,⁴,⁵ Opioids stimulate presynaptic m and k receptors on these axons which inhibit the release of the stimulatory neurotransmitters.⁶,⁷ Ketamine is a non-competitive antagonist at NMDA-receptors⁸ and is analgesic in subanaesthetic doses.⁹ Small doses of co-administered morphine and ketamine may be required to produce the endpoint i.e. analgesia, but with a better side effect profile.

The aim of this study was to compare the quality of analgesia provided by morphine and low dose morphine plus ketamine during patient controlled intravenous analgesia (PCIA).

Patients and methods
The study was approved by the Ethics Committee of the University of Pretoria. Thirty-six ASA I and II patients aged 18 to 60 years scheduled for elective abdominal hysterectomy were included. The study was double blind. Patients were randomised into Group M or Group MK. Group M received PCIA consisting of morphine 21 µg/kg with a lockout period of 7 minutes. Group MK received PCIA consisting of morphine 7 µg/kg plus ketamine 14 µg/kg with a lockout period of 7 minutes. Both groups received a standardised anaesthetic consisting of propofol 1 to 2 mg/kg, vecuronium, sufentanil, and isoflurane. Sufentanil 0.2 µg/kg was administered at induction and 0.1 µg/kg when more than 1.5 MAC isoflurane (end tidal concentration) was needed to keep the mean arterial blood pressure lower than 115% of the preoperative mean arterial pressure. Patients with allergy, asthma, nausea, vomiting, dreaming, hallucinations, pruritis, a history of drug abuse, psychosis or participation in any clinical trial during the previous three months were excluded.

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Postoperatively patients received morphine 30 µg/kg (Group M) or morphine 10 µg/kg plus ketamine 20 µg/kg (Group MK) every 10 minutes until they were pain free. PCA consisted of a bolus of morphine 21 µg/kg (Group M) or morphine 7 µg/kg plus ketamine 14 µg/kg (Group MK); the lock out time was 7 minutes in both groups. No other analgesics were allowed.

The following measurements were made: Sufentanil dose, morphine consumption during the first and second 24 hours, number of PCA requests, pain score (Visual Analogue Pain Score, VAPS), verbal descriptive sedation score (VDSS), haemoglobin saturation on the pulse oximeter at room air (SpO2), respiratory rate (RR). These were done preoperatively and 1, 4, 24 and 48 hours postoperatively.

Statistics
Null hypothesis: The quality of analgesia provided by morphine or low dose morphine plus ketamine do not differ. The response variable was the VAPS. Calculation of the sample size made use of the expected variation (standard deviation = total variation/6), i.e. the range of pain associated with the different treatments. For a standard deviation of 10 mm, resulting from a expected pain range of 60 mm, and an equivalence delta of 10 mm, a sample size of 36 subjects has a power of 80% at the significance level of 0.05.

All continuous variables were analysed using the Student t test for unequal variance (Welch). Discrete variables were analysed using Fischers exact test. Testing was done at the 0.05 level of significance. At each point in time (1, 4, 24 and 48 hours) Groups M and MK were compared with respect to the continuous variables VAPS, SpO2 and RR, using analysis of covariance (ANCOVA) with morphine consumption in the appropriate 24 hour period and VAPS as covariates. SpO2 and RR were analysed with VAPS as the covariate. Equivalence of the two groups was assessed by comparing the 95% confidence interval (CI) for the effect with the equivalence delta (10%).

Results
There was no significant difference between Group M and MK in age (39.33 years vs. 39.39 years; p = 0.9781), body mass (72.06 kg vs. 73.39; p = 0.7786), duration of surgery (102.50 min vs. 100.56 min; p = 0.8476) and sufentanil dose (0.189 µg/kg vs. 0.205 µg/kg; p = 0.5269).

Group MK used significantly less morphine than Group M during the first 24 hours (885.74 µg/kg vs. 0.205 µg/kg; p = 0.0316), as well as during the second 24 hours (264.89; 413.44; p = 0.0373). The morphine dose in both groups was significantly higher during the first than during the second 24 hour period (p < 0.001). The total number of boluses was significantly higher in Group MK than in Group M (394.5 vs. 156.5; p = 0.0057). Within the groups, there were significant differences in the number of boluses between the first and second 24 hours (p < 0.001) (Table 1, Figure 1).

In both groups, the mean pain scores (mean of VAPS at rest and during movement) were the highest at 1 hour. The mean VAPS did not differ significantly between groups at 1, 24 and 48 hours, but was significantly lower in Group M than in Group MK at 4 hours (22.36 mm vs. 38.33 mm; p = 0.0113). Although VAPS was not statistically significantly different between groups at 1, 24, and 48 hours, the criterion for equivalence (10%) was not reached. If the equivalence delta is set at 15%, pain scores were nearly equivalent at 24 hours and at 48 hours (Table 1, Figure 1). In Group M the pain score was significantly lower at 4 hours than 1 hour (p = 0.0128), but in Group MK the pain scores did not differ between 1 hour and 4 hours (p = 0.7035). In both groups, pain scores decreased after 1 hour with scores signifi-
significantly lower at 24 hours than at 4 hours and at 48 hours significantly lower than at 24 hours. In both groups pain scores were still significantly higher at 48 hours than preoperatively (p < 0.05). In neither Group M nor Group MK was any significant correlation (Spearman) found between VAPS at 1, 4 and 24 hours, and the number of boluses during the first 24 hours, or between VAPS at 48 hours and the number of boluses during the second 24 hours.

The number of boluses was significantly higher in Group MK during both the first and second 24 hours (Table 1). As the number of boluses determine the morphine consumption, the contribution of ketamine to analgesia must be determined, i.e. would the number of boluses differ had the bolus in both groups contained the same morphine dose? In order to investigate the influence of ketamine on pain scores at each of the postoperative times, ANCOVA was used with morphine consumption, adjusted for the first (754.86 µg/kg) and second 24 hours (340.67 µg/kg) as covariates. With ANCOVA, the mean VAPS at 4 hours was still significantly higher in Group MK than in Group (36.94 mm vs. 23.23, 75; p = 0.0450). Apart from VAPS at 4 hours, the therapies may be regarded as equi-analgesic (Table 2).

Figure 2: SpO2 at different times. The saturation was marginally significantly higher in Group MK at 4 hours (p = 0.0809*). Time 0 = preoperative

<table>
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<th>Variable</th>
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Discussion

The choice of doses of combinations of analgesics is hampered by a lack of information regarding interactions (pharmacodynamic and pharmacokinetic) between analgesics. In this study we investigated the analgesic interaction of morphine and ketamine. The VAPS did

Table 2: Influence of ketamine on VAPS, SpO2, and RR with morphine dose and VAPS as covariates.

- The lowest SpO2 occurred at 4 hours and 24 hours (Table 1, Figure 2). In order to investigate the influence of ketamine on SpO2 and respiratory rate at each of the postoperative times, ANCOVA was used with the morphine consumption adjusted for the first (33.33 mm), 4 hours (30.34 mm), 24 hours (21.32 mm) and 48 hours (12.50 mm) as covariates. With morphine as covariate, the marginal significant difference in SpO2 4 hours disappeared (p = 0.2660). With the relevant morphine dose as covariate, the RR at 4 hours was now marginally significantly higher in Group MK (p = 0.0860) but can still be regarded as equal to the RR in Group M (Table 2). With VAPS as covariate, SpO2 was always higher in Group MK, but the difference was never statistically significant. Ketamine therefore seems to have had a positive, however no statistically significant effect on SpO2. If the patients in the different groups had the same VAPS at the different times, the respiratory rate would also not have differed at any stage. Therefore, with the morphine dose as covariate, the marginally significant difference in SpO2 between Groups MK and M disappeared but a significant difference in respiratory rate at 4 hours appeared, and with the VAPS as covariate, no significant difference in respiratory rate or SpO2 between groups was found; the lower dose of morphine and not the amount of pain was therefore probably responsible for the higher respiratory rate and SpO2 in Group MK. There was no significant difference in sedation scores (VDSS) between groups at any stage. No sedation of VDSS > 2 was observed. No statistical significant difference was detected between groups in the incidence of nausea and vomiting, pruritis or dreaming and hallucinations at any of the times.

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Discussion

The choice of doses of combinations of analgesics is hampered by a lack of information regarding interactions (pharmacodynamic and pharmacokinetic) between analgesics. In this study we investigated the analgesic interaction of morphine and ketamine. The VAPS did
not reach equivalence (within 10%) at any stage of the study, with
Group MK experiencing more pain. The morphine consumption was
significantly lower in Group MK; 29% lower in the first 24 hours and
35% lower in the second 24 hours, taking into account that Group MK
requested many more boluses during both the first and the sec-
ond 24 hours. Apart from the significantly higher VAPS in Group
MK at 4 hours, the VAPS did not differ significantly (Table 1).
ANOVA showed that Group MK would experience significantly
more pain than Group M at 4 hours, even if they had received the
same dose of morphine during the first 24 hours. It thus appears as
though ketamine had some anti-analgesic effect at 4 hours (Table 2).
Using the significance level for statistical significant difference, out-
come parameters VAPS, VDSS, SpO2, and respiratory rate did not
differ between groups (apart from lower VAPS and SpO2 in Group M
at 4 hours), the study partly confirms the null hypothesis, namely that
the two PCA techniques are equivalent in the doses used. However,
when equivalence of the two groups was assessed using an equiva-
ence delta of 10%, Group M experienced less pain, used more mor-
phine, and less boluses than Group MK, while the side effects did not
differ significantly. The two analgesic regimens can therefore, in the
doses used, not be regarded equivalent (Table 1).

The number of boluses demanded by patients in Group MK was
significantly higher than those in Group M during both the first and
the second 24 hours. It may be that the analgesia produced by the
lower dose of morphine in Group MK was shorter lived than was the
higher dose in Group M. In spite of the significantly higher number
of boluses in Group MK, the total dose of morphine was both clini-
cally and statistically lower in Group MK than in Group M. The higher
number of boluses in Group MK may be ascribed to amnesia. This
might have caused the patient to forget that she had already pushed
the button and then would push it again. On the other hand, tolerance
to ketamine, or even in these early stages, drug seeking behaviour
might have emerged. If the latter had been the case, one would expect
the number of demands to increase with time. As this was not the
case, the higher number of boluses in Group MK was unlikely to
have resulted from the development of tolerance, or drug seeking
behaviour.

The total lack of correlation between the VAPS at 1, 4 and 24
hours and the number of boluses during the first 24 hours or the VAPS
at 48 and the number of boluses during the second 24 hours casts
doubt on the applicability of PCA in the population used (often an
inability to communicate due to language barriers). It has been noted
that some patients push the button when they think of it, demonstrate
it to visitors, etc.

The differences in VAPS and the number of boluses may have
been caused by sedation caused by morphine. In this study no differ-
ce in sedation was found. The significantly higher number of bo-
luses and VAPS in Group MK might have been caused by subjective
side effects (strange feelings) of ketamine – even at analgesic lev-
elS.11

The changes in the morphine dose from the first 24 hours to the
second 24 hours was -53,7% in Group M and -57,3% in Group MK
(p = 0,7804). This difference was not significant. It is thus unlikely
that the morphine sparing effect of ketamine involved the develop-
ment of tolerance in the short term. The long-term effect of ketamine
was not included into this study. It is therefore not possible to draw
any conclusion about the possible effect of ketamine on tolerance to
opioids. As neither pain scores nor the incidence of side effects dif-
fered significantly, it can be concluded that the quality of analgesia
rendered by the two techniques was equivalent.

As sole analgesic ketamine is analgesic at about 360 µg/kg/hour
and morphine at about 180 µg/kg/hour. If these drugs were synergis-
tic, co-administration of about a third of these doses might have pro-
duced adequate analgesia, avoiding their dose dependent side effects.
However, if drugs share the same side effect, these side effects may
also be more pronounced in combination.

Several investigators have studied the co-administration of mor-
phine and ketamine. Subcutaneous ketamine infusion (250 µg/kg
followed by 100 µg/kg/hour) provided significantly better quality of
analgesia than intravenous morphine (100 µg/kg followed by 100
mg/kg/hour) for the non-surgical care of musculoskeletal trauma. None
of the ketamine patients requested additional morphine during treat-
dment of fractures (splitting, manipulation, etc.).14

The superior analgesia provided by the combination of morphine
and ketamine reported by Javery et al10 and Adriaensson et al15 was
achieved at larger doses of morphine and ketamine, namely 100 µg/
kg/hour of each and morphine PCA in combination with a constant
ketamine infusion 150 µg/kg/hour respectively. Javery et al used
morphine and ketamine in equal doses (100 µg/kg/hour of each).
Adriaenssen et al used morphine patient controlled analgesia (1 mg
every 8 minutes; maximum of about 70 µg/kg/hour) in combination
with a constant ketamine infusion (150 µg/kg/hour). At 1 hour post-
operatively the morphine group experienced more pain than the
ketamine plus morphine group (5,4 mm vs. 2,5 mm). Although the
difference was statistically significant (p < 0,01), we do not regard
the difference as clinically of note. The cumulative morphine con-
sumption from 24 hours onward was significantly lower in the mor-
phine-ketamine group. This finding is in accordance with our find-
ings.

Edwards et al investigated the effect of ketamine on analgesia and
lung function in elderly patients. They combined morphine PCA in-
fusion of 1 mg/hour (14 µg/kg/hour) with ketamine 5 mg/hour, 10
mg/hour, or 20 mg/hour (54 µg/kg/hour to 468 µg/kg/hour adjusted
for body mass). There was an increase in postoperative dreaming but
without significant difference in morphine consumption or postop-
erative analgesia or lung function. No significant correlation was found
between the ketamine dose and morphine consumption.17 Inspection
of their data suggests that a substantial number of patients experi-
enced moderate to severe pain at 4 hours and 8 hours postoperatively.
It therefore seems that the ketamine doses were too low to add to the
analgesia provided by the low dose of morphine (14 µg/kg/hour).
Owen et al found that analgesic levels of ketamine (100 µg/l to 150
µg/l) could be achieved by an infusion of 240 µg/kg/hour.18 A sub-
cutaneous infusion of morphine 40 µg/kg/hour plus ketamine 600
µg/kg/hour has been found to provide reliable analgesia after abdomi-
nal hysterectomy.20

The question thus arises, whether the maximum doses of mor-
phine and ketamine allowed in Group MK (60 µg/kg/hour and 120
µg/kg/hour respectively) were efficient to ensure adequate analgesia.
Taking the findings of previous studies into account, it seems as though
the doses of both morphine and ketamine were too low in Group MK.
The significant difference in VAPS between MK and M might have
been smaller had the morphine and ketamine doses been higher,
say in the order of 90 µg/kg/hour and 180 µg/kg/hour respectively
(about 11 µg/kg and 22 µg/kg with a lock out period of 7 minutes).
These doses represent an additive rather than a synergistic interaction
between morphine and ketamine.

Theoretically, any drug with opioid sparing properties may attenuate
the development of tolerance. Kissin has shown that ketamine in
subanalgesic doses decreased alfentanil consumption in rats. He is of
the opinion that ketamine attenuates the development of acute toler-
ance to alfentanil, as the ketamine dose was too small for any direct
antinociceptive action.21

The effect of ketamine on ventilation is uncertain. Both stimulation22 as well as depression23 of ventilation has been reported. In this study ANCOVA revealed that the reason for the difference in respiratory rate at 4 hours can be the presence of ketamine, and that the difference in SpO2 disappeared if the two groups had received the same dose of morphine. As the morphine consumption was significantly lower in the morphine-ketamine group during the first 24 hours, as well as over 48 hours, while the VAPS did not differ significantly (apart from VAPS at 4 hour), the presence of ketamine in Group MK contributed significantly to analgesia, while attenuating the effect of morphine on SpO2 and RR.

The effect of ketamine on respiratory rate is in accordance with the findings of Presson et al.24 They found that analgesic concentrations of ketamine antagonized alfentanil-induced hypventilation. Alfentanil induced a decrease in respiratory rate, without affecting tidal volume and respiratory drive. They ascribe the effect of ketamine on ventilation to two possible mechanisms. Firstly, ketamine caused subjective side effects in all subjects (e.g. strange feeling, body feels tight, arms and legs strange, body feels heavy, etc) that might have caused general arousal, thereby stimulating respiration indirectly. Secondly, being an NMDA receptor antagonist, ketamine may antagonize the effect of opioids on ventilation as the effect of opioids on the control of breathing may be through inhibition of glutaminergic transmission.25,26

No dreaming or hallucinations was reported. The ketamine dose was therefore high enough to have a morphine sparing effect, but lower than a dose that causes hallucinations. It is accepted that affective disturbances may affect pain experience. Subjective side effects of ketamine might have had an influence on the VAPS in this study. Apart from hallucinations, patients were however, not questioned about these side effects. This aspect should be taken into account in studies of this nature.

Conclusion

The low dose ketamine-morphine combination can, in the doses used, not be regarded as equal but rather inferior to morphine PCA, but it may reduce the profile of respiratory side effects of morphine. The analgesic effects of morphine and ketamine are additive rather than synergistic. In appropriate doses morphine-ketamine combinations may find application in other fields of pain therapy, for example obstetrics and cancer, and deserve further investigation.

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