

CLINICAL STUDY REGARDING PREEMPTIVE ANALGESIC EFFECT OF KETAMINE AND REMIFENTANYL IN LAPAROSCOPIC CHOLECYSTECTOMY

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Abstract

Pain modulation is related to an equilibrium between antinociceptive and pronociceptive systems. Therefore, the apparent pain level could not only be a consequence of a nociceptive input increase but could also result from a pain sensitization process. Glutamate, *via* N-Methyl -D-aspartate (NMDA) receptors, plays a major role in the development of such a neuronal plasticity in the central nervous system, leading to a pain hypersensitivity that could facilitate chronic pain development. By acting on both NMDA and opioid receptors we can get analgesic effect and prevent chronic pain development.

According to these aspects, a clinical study estimating preemptive analgesia with ketamine and remifentanyl in laparoscopic cholecystectomy was designed and carried out.

A number of 112 patients divided in five groups were analysed regarding efficiency and safety aspects. All the patients received the same dose of remifentanyl and different doses of ketamine.

The results of the study indicated the best analgesic effect within the group in which the patients received 0.75 µg/kg/min remifentanyl from induction of anaesthesia until suture and ketamine was given in doses of 10 µg/kg/min from induction of anaesthesia and six hours in the postoperative period.

Concerning the safety aspect of this scheme the result was less satisfying.

Rezumat

Modularea durerii reprezintă un echilibru între sistemele antinociceptive și cele pronociceptive. Creșterea intensității durerii nu este doar consecința impulsurilor nociceptive, este și consecința sensibilizării centrale. Glutamatul, prin receptorii săi N-Metil-D-aspartat (NMDA), joacă un rol important în dezvoltarea plasticității neuronale conducând la hipersensibilizare centrală cu instalarea durerii cronice. Receptorii NMDA precum și receptorii opioizi modulează efectul analgezic și reduc sensibilizarea centrală, ceea ce previne instalarea durerii cronice.

Pornind de la aceste premize, am inițiat și desfășurat un studiu clinic de evaluare a analgeziei preemptive cu ketamină și remifentanil, în colecistectomiile laparoscopice. Am urmărit eficiența și siguranța, la 112 pacienți repartizați în cinci grupuri, diferențiate prin alternativele de inducere a analgeziei preemptive. Rezultatele studiului au evidențiat ca

metodă de analgezie preemptivă superioară în privința eficienței pentru colecistectomiile laparoscopice, următoarea schemă antialgică: remifentanil 0.75 µg/kg/min administrat de la inducția anesteziei până la sutură și 10 µg/kg/min administrate de la inducția anesteziei până la șase ore postoperator.

Această schemă a fost însă mai puțin satisfăcătoare în privința siguranței.

Keywords: ketamine, remifentanyl, preemptive analgesia, laparoscopic cholecystectomy

Introduction

Ketamine is a medicine that has been used in clinical practice for a very long time. It has been known as a drug that provides “complete” anesthesia in that it combines sedation, amnesia and pain relief. At the same time it has less tendency to depress airways reflexes than some other commonly used anesthetic agents. It also increases heart rate, blood pressure, and secretions [1, 6].

It seems to have fallen out of favor for its every day use as a drug in the same class as the “street drug”; it is well known to cause hallucinations and nightmares in some settings. Lately, it seems to have gained some stigma because of its common use in veterinary medicine. [8, 9].

This article is not intended to argue for or against its place in the delivery of anesthesia today. Researchers are trying to find new possible uses for ketamine that might be used more in the future as a “niche” than it has been nowadays [2, 3].

Ketamine provides analgesia via a different mechanism when compared to opioids. Its antagonist action on N –Methyl –D aspartate (NMDA) receptors has beneficial effects. For example it is a common clinical observation that some patients have opioid- resistant pain. This resistance is due to the activation of NMDA receptors in perioperative period.

Ketamine may prevent central sensitization during surgery and results in preemptive analgesia. The reliability of preemptive analgesia however is controversial. The real challenge, however, in the clinical setting might not be to use the least amount of analgesic drug but to minimize long term complication and occurrence of chronic pain syndromes. The studies, would have gained in interest if they had focused more on the long-term follow-up of the patients using clinical assessment of allodynia and hyperalgesia [4, 5].

Many studies have reported that ketamine effects are elicited when this drug is administered in subanesthetic doses. The optimal dose of ketamine as an adjunct to peripheral nerve block is unknown. It was found that ketamine in subanesthetic doses improved postoperative pain

management by reducing hyperalgesia due to both surgical trauma and high perioperative opioid doses. This antihyperalgesic action of ketamine also limited the postoperative morphine tolerance leading to a decrease in analgesic consumption and an increase in the analgesia quality.

A prospective study was performed at the Surgery Clinic of the Emergency Clinical Hospital Bucharest, Romania estimating preemptive analgesia with remifentanyl and ketamine regarding efficiency and safety aspects.

Materials and methods

A number of 112 cholecistectomy patients were given preemptive analgesia consisting of *i.v.* low doses of ketamine and remifentanyl.

Patient's written, informed consent was obtained before surgery and the clinical study was approved by local Hospital Ethics Committee.

112 patients scheduled for laparoscopic cholecistectomy were divided into five groups. The groups were completed in time separately. The first, Group A (36 patients) was regarded as the control group and received remifentanyl 0.75 µg/kg/min from induction toward the end of anesthesia and 20 mg morphine at the end of surgery. Group B (29 patients) received 10 µg/kg/min ketamine and remifentanyl 0.75 µg/kg/min from incision until suture. Group C (19 patients) received 25 µg/kg/min ketamine from incision until suture and remifentanyl 0.75 µg/kg/min. Group D (3 patients) received 100 µg/kg/min ketamine from incision until suture and remifentanyl 0.75 µg/kg/min. Group E (25 patients) received remifentanyl 0.75 µg/kg/min from induction of anesthesia till the end of anesthesia and 10 µg/kg/min ketamine during the anesthesia and for the first six hours postoperative.

Because of the side effects we decided to stop group D, after only 3 patients enrolled (see Results and discussion).

General anesthesia was induced with propofol and midazolam. Suxamethonium was given to facilitate endotracheal intubation. The neuromuscular block was continued with mivacurium chloride. Anesthesia was maintained with isoflurane. At the end of anesthesia residual neuromuscular block was antagonized with *i.v.* neostigmine.

In the postoperative ward the following parameters were recorded for 48 hours:

- time to the first analgesic demand;
- pain intensity by VAS (Visual Analogue Scale) and verbally;
- patient behavior while in pain [2];
- total analgesics consumption;
- hemodynamic status;

- general health within 24 hours postoperative was related to mobility, self-care, usual activities (reading, watching TV, socialization), discomfort, anxieties/depression;
- ketamine and remifentanyl were related to symptoms distress scale such as nausea, vomiting, delirium, hallucination [10];
- on the day of the patients discharge they were asked to give their opinion regarding their state of health by pointing on the scale marked from 0 to 100;
- on the same day of the patients discharge they were asked to fill in the global satisfaction treatment scale according to different degrees of satisfaction such as very satisfied, satisfied, minimally satisfied, neither satisfied nor dissatisfied, minimally dissatisfied, dissatisfied, very dissatisfied.

The results were assessed using a GraphPad software method.

Results and discussion

Three patients were included in Group D, received 100 µg/kg/min ketamine and remifentanyl 0.75 µg/kg/min from incision until skin closure. For all patients awakesness from anesthesia was very difficult, taking between 60-90 minutes for recovery. All of them presented bronchospasm. As a consequence we decided to stop this group and to exclude it from our study and to continue with groups A, B, C, E.

The intensity of pain measured by VAS (10cm horizontal assessment scale on which the least possible pain is marked 0 and the worst possible pain is marked 10) among groups was 3.5 in Group A, 2.72 in Group B, 3.39 in Group C and 3.76 in Group E. No significant differences ($p>0.05$) were registered in pain scores of the four groups during the study period (Figure 1).

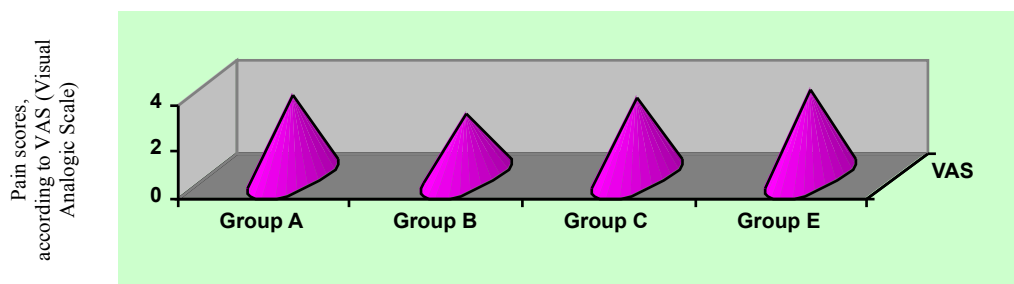


Figure 1
Intensity of pain measured by VAS (Visual Analogue Scale)

The time until the first demand for analgesics among the four groups was Group A 6.88 hours, Group B 7.99 hours, Group C 3.17 hours, Group E 20.62 hours (Figure 2). An extremely significant difference was registered among Group C and Group E, Group A and Group E. and between Group B and Group E ($p < 0.0001$). No significant difference among Group C and Group A or Group B and between Group A and Group B was noted ($p > 0.05$).

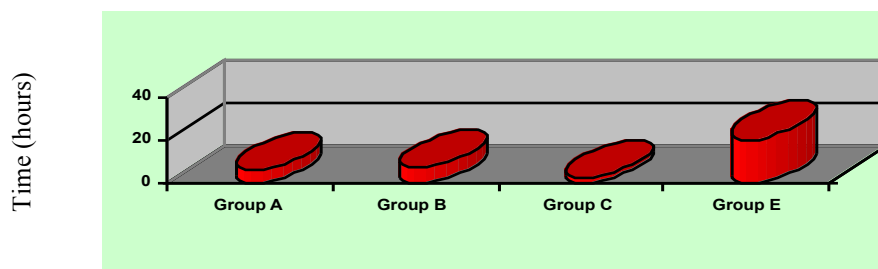


Figure 2

The time (hours) until the first demand of analgesic in postoperative period

The total analgesic consumption was 2.11 doses administrated in Group A, 2 doses in Group B, 1.73 doses in Group C and 1.2 in Group E. We could say that the total analgesic consumption decreased from Group A to Group E. with significant difference ($p < 0.0001$) (Figure 3).

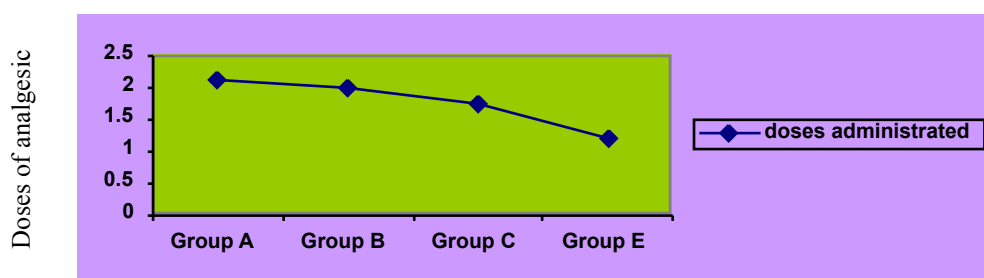


Figure 3

Total analgesics consumption among the studied groups

Nausea and vomiting were present in all groups.

The incidence of hallucination and delirium were present only in Group E (10 patients). Three of the patients lived an experience like "being in the K-hole", with the sensation of rising above their body, inner peace, radiant light visual perception and sense of touch were amplified, feeling "floating" - slightly or far away from their body, numbness in their

extremities, visual distortions, lossing the sense of time, senses, and identity, euphoria, confusion, visual perception and sense of touch were amplified.

Two of the patients felt energized after the ketamine experience and had a strong urge to move around and talk with persons around them.

Four of the patients had urinary difficulties and needed a urinary device which delayed mobilization in postoperative period for over 24 hours. Literature does not provide a lot of information in this aspect. The results of a study, published in the Hong Kong Medical Journal [11], following a small group of users who had been involved with the drug over a four-year period concluded that ketamine was responsible for causing bladder and kidney damage. This study, also suggest that the urinary tract infections are very common among ketamine users and drinking cranberry juice may help to prevent this side effect [11].

Other symptoms like hypoglycemia, nystagmus, bizarre postures, monosyllabic mumble were presented in one patient that determined us to stop administration of ketamine three hours later.

Conclusions

We can conclude that the preemptive use of ketamine and remifentanyl in doses similar to those of group E significantly reduces postoperative pain and reduces analgesics consumption in the postoperative pain management. The preoperative administration of ketamine and remifentanyl in patients undergoing laparoscopic cholecistectomy determined a preemptive analgesic effect under the efficiency aspect.

Concerning the safety aspect of the study we consider that it should be continued with other new groups using lower doses of ketamine in order to establish the antihyperalgesic dose of ketamine which could reduce its side effects.

However, the suggestion that a very low dose of ketamine (low enough to avoid side effects) might have significant implications for post-operative care is once again intriguing.

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