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Comparing the Effect of Adding Ketamine and Neostigmine to Bupivacaine 0.25 % for Epidural Analgesia among Patients Candidated for Elective Femoral Fracture Surgery

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ABSTRACT

Pain is a complex medical problem that its inadequate postoperative control has adverse effects on patients' physiological, metabolic and mental status. Adding new supplements will lead to an increased duration of analgesia. The purpose of this study was to compare the addition of neostigmine and ketamine to bupivacaine 0.25% for epidural analgesia increasing duration of postoperative analgesia. In this double blind clinical trial, 90 patients over 50 years candidated for elective hip surgery with ASA class I, II were randomly divided to three groups: neostigmine, ketamine and control groups. All patients received epidural with bupivacaine 0.25% by 2cc/segment. Furthermore, 60 micrograms neostigmine was added in first group and 40 mg ketamine was used for group II. Level of postoperative pain based on VAS and duration of analgesia and amount of analgesic was determined and compared across the three groups. The mean of pain score at 6 and 12 hours after surgery was significantly lower in the ketamine group than the other groups and in neostigmine group was less than placebo ($P \leq 0.01$). The mean of duration of postoperative analgesia in the ketamine group was significantly higher than the other groups and in neostigmine group was more than placebo ($P \leq 0.01$). The mean dose of analgesic (pethedin) was the least in the ketamine group ($P \leq 0.001$). Neostigmine and ketamine with bupivacaine 0.25% for epidural anesthesia increased the duration of analgesia during the postoperative period and reduced analgesic consumption that about ketamine was more than neostigmine.

Keywords: Neostigmine, Ketamine, Epidural, Analgesia after Surgery.

INTRODUCTION

One of the common medical problems in the field of treatment is bone fracture. Femoral fractures are quite common. According to the modern day Orthopedics, all femoral fractures require operation and Fixation. On the other hand, the occurrence and intensity of pain among these patients is really high [1]. Various studies have pointed to the fact that during and after complete replacement of hip joint using regional anesthesia (spinal or epidural), bleeding among the patients will decrease as much as 30 to 50 percent and it is really effective in controlling post-operative pain as long as 24 to 72 hours [2 & 3].

One of the major advantages of regional anesthesia is that it can remove the post-operative pain without need for further narcotics (either by itself or mixed with general anesthesia). This will help the patients start moving faster, be discharged more quickly and spend less money on their treatment. This is very important in terms of physical, mental and economic factors [2].

The type of medicine also influences the analgesic ability after epidural operation and moderation of pathophysiologic response and will result in an improved state. For instance, the local anesthetics used in regional methods will result in quicker restoration of digestive motions and have less pulmonary side effects and provide better analgesia compared to systematic venous opioids. The advantages of post-operative epidural analgesia may result in further satisfaction of patients and improve their life quality.

Large researches are being carried out on medical alternatives as the main Neuraxial analgesic medicine and supplementary medicines beside the main drugs.

These adjuvants are used beside local anesthetics to improve analgesia and reduce the side effects, but none could achieve a general acceptance. Neostigmine and ketamine are two drugs recently used as adjuvant medicines. Despite their exciting theoretic effects, few clinical studies have been conducted on them. Neostigmine increases the level of analgesia and its duration by releasing nitric oxide in spinal cord. The other mechanism proposed for it deals with harnessing Acetylcholinesterase and increasing the density of acetylcholine in spinal cord. Muscarinic receptors in the posterior horn of spinal cord increase the pain threshold and analgesia. Ketamine is another adjuvant drug whose popularity as a means to control pain is on the rise. Its effects are mainly attributed to its antagonistic properties on NMDA (n-methyl-d-aspartate) receptors. It can be really effective in moderating central sensitization and opioid resistance.

Taking into consideration all these interpretations, we seek to study the effect of neostigmine and ketamine as adjuvant drugs beside bupivacaine for elective surgery in femoral fractures.

MATERIALS AND METHODS

This is a double-blind, randomized clinical trial registered under the trial code IRCT201112198468N1 conducted on patients with femoral fractures candidated for elective surgery. Having obtained informed consents, as many as 90 patients over 50 with femoral fractures candidated for elective surgery who had class 1 and 2 ASA who had no history of allergy to local anesthetics were randomly divided into three groups (30 in each group): A (neostigmine), B (ketamine), and C (placebo). Firstly, all the patients were injected with 5 cc/kg Ringer Lactate serum 10 to 15 minutes before operation in order to achieve the sufficient hydration (as CVE: Compensatory intravascular volume expansion). The patient was then asked to assume a sitting position and a No. 19 needle was used to conduct epidural anesthesia through L5-L4 or L5-S1. The desired material was injected after entering the epidural space. All three groups received as much as 2 cc/segment of 0.25% bupivacaine. Group A received 60 μg neostigmine, while 40 mg ketamine was used for group B. Distilled water was used to increase the final volume of the solution to 20 cc for all three groups. All patients received 2 mg midazolam for sedation. During operation, ringer solution was used to make up for the liquids the patients would lose. Those patients whose operation lasted longer than 120 minutes or experienced severe bleeding or required transfusion or their epidural anesthesia failed were excluded from our research. The pain score of all patients in recovery within 6, 12, and 24 hours after operation was measured and specified based upon VAS ruler. The time for primary painkiller request (pethidine in the case of this research) and the dose of painkiller used during 24 hours and during the period of analgesia and the average blood pressure, heart rate, ECG status and percentage of oxygen saturation before conducting epidural and right after it and every 5 minutes during the operation (maximally 120 minutes) were registered. The painkiller used in this research was pethidine prescribed for patients in milligrams.

A questionnaire containing questions on the hemodynamic status of patient and pain score and the length of analgesia was filled and the information obtained was statistically analyzed.

The K-S test was used to study the normal distribution. Independent t-test was used to study those variables which had a normal distribution, while Mann-Whitney U was used to study the variables which had an abnormal distribution. Having entered the information in a statistical software, the information were represented in the form of tables and charts, and analytical statistics including mean difference comparison test in two groups of independent t-test (Mann-Whitney U) and successive test measurement were utilized.

RESULTS

The effects of adding neostigmine and ketamine to 0.25% bupivacaine on post-operative analgesia with epidural anesthesia among femoral fracture elective patients are presented here:

Of all the 30 patients studied in neostigmine group (A), 54.6% were male and 45.4% were female. Of all the 30 patients studied in ketamine group (A), 59% were male and 41% were female. In the placebo group, 59.1% were male and 40.9% were female. No statistically significant difference was observed between the three groups in terms of gender distribution. As $P \geq 0.05$, the gender distribution in all three groups was equal and nearly 55.1% of participants in all three groups were male (table 1-4).

Table 1: Comparing the genders across three groups of neostigmine, ketamine and placebo among patients with femoral fracture

Gender / group	Male	Female	Total
Neostigmine	54.6%	54.4%	100%
Ketamine	59%	41%	100%
Placebo	59%	40.9%	100%
Total	55.1%	44.9%	100%

Table 2: Comparing the average age across three groups of neostigmine, ketamine and placebo among patients with femoral fracture

Age / group	Average age (years)
Neostigmine	66.3
Ketamine	67.4
Placebo	65.5
Total	66.4

Table 3: Comparing average pain score in recovery 6, 12, and 24 hours following operation among the three groups of patients with femoral fracture

Group / hour	Recovery	After 6 hours	After 12 hours	After 24 hours
Neostigmine	0.22	1.05	2.82	4.10
Ketamine	0.13	0.90	2.63	4.04
Placebo	0.18	1.77	4.03	4.18
Statistical test	Mann-Whitney U	Mann-Whitney U	Mann-Whitney U	Mann-Whitney U
P-value	$P \geq 0.05$	$P \leq 0.01$	$P \leq 0.01$	$P \geq 0.05$

Table 4: Comparing average length of analgesia among the three groups of patients with femoral fracture

Group	Length of analgesia (hours)	Statistical analysis
Neostigmine	9.30	$P \leq 0.001$ Anova test
Ketamine	10.15	
Placebo	5.30	

According to table 2, the following average ages were reported for different groups: 66.3 years for neostigmine group, 67.4 years for ketamine group, and 65.5 for placebo group. As $P \geq 0.05$, there is no significant difference between the three groups in terms of age and the average age of the three groups was 66.4 years (tables 2-4).

As $P \geq 0.05$, no statistically significant difference was observed between the three groups in terms of the average pain score in recovery. However, pain score in ketamine group was less than what was observed in the other two groups 6 and 12 hours after operation. This score in neostigmine group was less than what was observed in placebo group ($P \leq 0.01$). No statistically significant difference was observed between the three groups in terms of pain score 24 hours after operation ($P \geq 0.05$) (table 3-4).

As it is shown in table 4, the average analgesia time was different across the three groups. As $P \leq 0.001$, the average length of anesthesia was significantly more than the two other groups, while the average length of analgesia in placebo group was the least.

The average dose taken within the first 24 hours following the operation was also different across the three groups. As $P \leq 0.001$, this dose was the least in ketamine group (33.3 mg pethidine) (table 4-5).

Table 5: Comparing average dose of painkiller taken within the first 24 hours following operation among the three groups of patients with femoral fracture

Group	Dose (mg)	Statistical analysis
Neostigmine	40.9	$P \leq 0.001$ Anova test
Ketamine	33.9	
Placebo	79.5	

The average pain score 6 and 12 hours after operation in ketamine group was significantly less than the other groups. In neostigmine group, this score was less than placebo ($P \leq 0.01$). No significant difference was observed between the score of three groups in recovery ($P \geq 0.05$).

DISCUSSION

What has always concerned the minds of anesthesiologists is development of an appropriate drug as a supplement to be added to local anesthetics in epidural block in order to lengthen the period of analgesia and increase patients' satisfaction. This research seeks to achieve an appropriate medical compound capable of elongating the length of analgesia through epidural method. Paying attention to Geriatric medicine and problems of their adjacent disease (considering the increasingly wide growth of this age group in society) seems to be one of the most important priorities of healthcare system. One of the most common types of fracture among this age group is femoral bone fracture. Utilizing regional techniques, particularly epidural anesthesia and post-operative pain control will provide major aid to doctors and it has great advantages for these old patients.

By adding ketamine and neostigmine as adjuvant beside local anesthetics for epidural anesthesia, the average post-operative analgesia lengths and scores were compared against one another. A comparison of the results achieved for neostigmine, ketamine, and placebo group clearly points to the fact that the average pain scores of three groups within 6 and 12 hours after operation were different and pain score in ketamine group was less than the other two groups. In ketamine group, the average period of post-operative analgesia was more than other 2 groups. This average in neostigmine group was more than what was observed in placebo group. The average dose of painkiller taken (milligrams of pethidine) within the first 24 hours after operation in ketamine group was also less than the other two groups.

There results of previous researches are partially in line with what we have achieved. In a study conducted by Batra et al (2003), it turned out that adding neostigmine to anesthetics as a supplement in Urogenital surgeries in children conducted through caudal anesthesia (it is in fact a kind of epidural anesthesia) helps make the length of post-operative analgesia among children longer [16].

In a similar research conducted by P.H. Tan et al (2000), it turned out that intrathecal neostigmine helps reduce post-operative pain in inguinal herniorrhaphy. In this research, the length of analgesia in neostigmine group was significantly longer than placebo ($P \leq 0.05$) [17].

In another research conducted by Z.H. Khan et al (2008) in India, it turned out that using intrathecal neostigmine sedated the pain following spinal disc operation and the score of pain in neostigmine group 4 and 8 hours after operation was much less than what was observed in placebo group. According to this research, the average amount of morphine used within the first 24 hours in neostigmine group was 0.9 mg, while this amount was 4.7 mg in placebo group [18].

In a study carried out by Liu S. et al (1995), adding ketamine could not increase the length of anesthesia significantly following an operation with epidural anesthesia. The results of that study was not in line with ours. This discrepancy may be attributed to different types of surgery, the small number of samples in previous research, and the type of medicine taken [5].

Considering all the consistencies referred to between our research and the above-said studies, it turned out that the length of analgesia in ketamine group is more than the other 2 groups. The length of analgesia in neostigmine group was more than what was observed in placebo group. The pain score and the average amount of painkiller taken within the first 24 hours following the operation in ketamine group was more than what was observed in the other 2 groups. This value in neostigmine group was less than what was observed in placebo group. All these facts point to

the positive and effective influence of using neostigmine and ketamine as adjuvant beside bupivacaine through epidural method among patients suffering from femoral fracture. Thus, the present research recommends using such drugs but emphasizes ketamine as the best supplement (with the minimum effective dose). No particular side effects in neostigmine and ketamine groups were observed. Furthermore, researchers are recommended to compare other adjuvants with drugs used in this research and report their results in order to achieve the best medical compound with the highest efficiency and least side effects.

CONCLUSION

Using neostigmine and ketamine as adjuvants along with 0.25% bupivacaine in epidural anesthesia results in a longer post-operative analgesia and less consumption of painkillers. A longer period of analgesia and less consumption of painkiller has been observed among those consuming ketamine compared to those who had taken neostigmine.

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