INTRA-ARTICULAR KETAMINE VERSUS INTRA-ARTICULAR NEOSTIGMINE TO ENHANCE ANALGESIA AFTER KNEE ARTHROSCOPY: A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

Background: Intra-articular drugs and local anaesthetics are the most popular methods for pain relief after arthroscopic knee procedure. Many drugs, including opioids, non-steroidal anti-inflammatory drugs, ketamine, clonidine, and neostigmine, have been used intra-articularly. Objectives: The aim of our study was to compare the analgesic effect of intraarticular injection of ketamine bupivacaine and neostigmine bupivacaine in patients undergoing arthroscopic knee surgery under intra-thecal anaesthesia. Design: a randomized controlled trial included 100 Patients were randomly divided into two groups 50 patients each, setting: the study was conducted in Assuit university tertiary hospital, Egypt. Interventions: Neostigmine group received intra-articular 0.5mg/dose neostigmine + 20 ml 0.25% bupivacaine and ketamine group received intra-articular 0.5 mg/kg ketamine + 20 ml 0.25% bupivacaine. VAS score was used for post-operative evaluation of pain every 4 hours over a 24 hour period. The total analgesic dose and any side effects were also recorded. Results: There were no significant differences in VAS score between the two studied groups but Time to rescue analgesia was significantly longer in the ketamine group (447.70±48.109 minutes) than in the neostigmine group (257.60±47.243 minutes) with P value ≤ 0.000. There was a significant difference in the analgesic dose of ketorolac between ketamine group and neostigmine group. Conclusion: Injection of intra-articular ketamine bupivacaine provided better postoperative analgesia, less side effects and lower supplementary analgesic dose than intra-articular neostigmine bupivacaine. Trial registration: This study is registered by the local research ethics committee and its Approval Number: IRB00008788 and registered at www.clinicaltrials.gov under number NO: NCT02720705. Key words: analgesic dose, intra-articular, ketamine, neostigmine

INTRODUCTION

Arthroscopic knee surgery is a common type of operative procedure nowadays and commonly performed as an outpatient procedure. Post-operative pain is a common cause of delayed discharge and ambulation. (1) Intra-articular (IA) drugs and local anesthetics is the most popular method for pain relief after arthroscopic knee procedure (2-4) Many different drugs, including opioids, non-steroidal anti-inflammatory drugs, ketamine, clonidine, and neostigmine, have been used IA.(5) In our study we compared intra-articular neostigmine versus ketamine for postoperative pain relief in arthroscopic knee surgery. Neostigmine is an anticholinesterase and has analgesic effects when administered intrathecally or peripherally. (6-9) a lot of mechanisms describe the peripheral analgesic effect of neostigmine such as decreasing release of pronociceptive neurotransmitters, hyperpolarization of neurons or activation of the nitric oxide-cyclic guanosine monophosphate pathway may mediate this peripheral analgesic effect by increasing endogenous acetylcholine. (10) Detection of N-Methyl-D-aspartate (NMDA) receptor and has a role in reducing the pain and the development of a new use of ketamine. The use of low dose ketamine as a NMDA receptor antagonist in relieving the pain and reducing the need for opioids. Ketamine blocks NMDA receptors in the posterior horn postsynaptic membrane of the spinal cord and inhibits the pain transmission through the pain fibers to the central nervous system, resulting in reduced pain or no pain sensation. Ketamine has a topical analgesic effect, Ketamine can be used in many routs such as intravenous, oral, intramuscular, intranasal, subcutaneous, or intra-anal or epidural and has rarely been used intra-articularly..(11, 12) Our study compared intra-articular neostigmine to intra-articular ketamine for post-operative pain relief in arthroscopic knee surgery. METHODS

This study was done in Assuit university hospital after approval of our local ethical committee approval Number: IRB00008788 and clinical trial registration NO: NCT02720705 and according to Helsinki declaration, in period from November 2013 to August 2014, a written informed consent was taken from all patients who agreed to participate in the study. One hundred adult patients aged between 18 and 45
years old of ASA I or II, undergoing elective arthroscopic partial meniscectomy under intra-thecal anaesthesia, were included in the study.

**Exclusion criteria:**

Absolute or relative contra-indications for intra-thecal anaesthesia, Allergy for the studied drugs. Patients having history of cardiovascular, cerebro-vascular or respiratory diseases. Patients receiving chronic pain treatment or hypertension treated with α methyldopa, clonidine or β adrenergic blockers were excluded from the study. On preoperative visits, the procedure was explained to patients and they were also taught to interpret the visual analogue scale (VAS) (graded from 0 = no pain to 10 = maximum pain).

In the operating room we used standard monitoring (ECG, pulse oximetry, Mean arterial blood pressure). The procedure was done under intra-thecal anaesthesia with 3ml of hyperbaric bupivacaine 0.5%. Patients were randomly distributed using an online research randomizer (http://www.randomizer.org) into two groups (50 patients each). Each group received either intra-articular dexametomidine or neostigmine. At the end of the procedure, one group received intra-articular Neostigmine 0.5mg/dose + 20 ml 0.25% bupivacaine and the other group received intra-articular ketamine 0.5 mg/kg + 20 ml 0.25% bupivacaine. Intra-articular solutions were injected into the knee joint through the cannular sheath after withdrawal of the camera, by the orthopedic surgeon (who was also unaware of the nature of the study drugs) before removal of the arthroscope. At the intra-operative period: mean blood pressure (MBP) and heart rate (HR) were recorded every 10 minutes. Duration of surgery and Tourniquet time recorded.

Post-operative assessment of each patient on his bed at inpatient ward every 4 hours over a 24 hour period. At each visit, heart rate (HR), mean blood pressure (MBP), arterial oxygen saturation (SaO2) were assessed. Patients also asked to describe the severity of their pain on a specific sheet included a visual analogue pain scale (VAS) and the need for analgesia if (VAS) was more than 3 also recorded and the dose of supplemented ketorolac if analgesia was needed. Sedation scores were recorded at 4th, 8th, 12th, 16th, 20th and 24th hours after discharging the patients from the operating theatre. The patients’ level of sedation was assessed using Ramsay sedation scale (RS), which is a simple scale, scored from 1 (patient anxious and agitated or restless or both) to 6 (no response to light glabellar tap).

Ketorolac 30 mg IV (With maximum dose 90 mg per day) was administered i.v. as an analgesic supplement if the recorded VAS pain scale was ≥ 3 and was repeated every 8 hours if required. The time to the first analgesic requirement and the total Ketorolac dose during the first 24 hours after operation were also recorded. Side effects such as nausea, vomiting, bradycardia (defined as HR < 45 beats /min), and hypotension (defined as reduction of MAP > 25% of baseline) were recorded. All data were collected by an observer who was unaware of patients’ group assignment.

**Statistical analysis:**

Calculation of exact sample size is an important part of any research design. It is very important to understand that different study design need different method of sample size calculation and one formula cannot be used in all designs. Our sample size was estimated using VAS pain scale as the primary variable. On the basis of a pilot study and assuming a standard deviation of 1 cm, 38 patients were required in each group to have an 80% chance to detect a difference of 1 cm on the VAS at the 5% level of significance. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Results for normally distributed continuous variables are expressed as mean± standard deviation. Categorical data and dichotomous variables were shown as number and percentage. Comparisons of continuous variables were performed using independent t-test. Proportions were compared with chi-square test. All reported P values are 2 sided with a significant α level of 0.05. Differences were considered to be statistically significant if the null hypothesis could be rejected with 95% confidence (p < 0.05). The SPSS ver.20 statistical software package (SPSS for Windows Release 20.0.0; SPSS Inc, Chicago, Ill, USA) ® package was used for statistical analysis.

**RESULTS**

Patients in the two groups were comparable as regard age, sex, duration of surgery and tourniquet time. There were no significant difference in demographic data (age –gender), operative time and tourniquet time between the ketamine group and the neostigmine group. (Table 1)
Table 1: comparison of age, gender, operative time and tourniquet time between ketamine and neostigmine groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Ketamine</th>
<th>Neostigmine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ages (yrs.)</td>
<td>30.16± 3.803</td>
<td>31.34± 5.093</td>
<td>0.192</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>46 (92%)</td>
<td>47 (94%)</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>operation time (min)</td>
<td>47.30± 12.706</td>
<td>51.00± 8.806</td>
<td>0.094</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>39.40± 11.368</td>
<td>44.60± 8.320</td>
<td>0.101</td>
</tr>
</tbody>
</table>

The intra-operative hemodynamic parameters (heart rate and mean arterial blood pressure) showed a non-significant difference between the ketamine group and the neostigmine group. The post-operative hemodynamic parameters (heart rate and mean arterial blood pressure) showed a non-significant difference between the ketamine group and the neostigmine group. There were no significant difference in VAS score between the ketamine group and the neostigmine group. (Figure 1)

Figure 1: VAS scores at different times of measurement in the ketamine and neostigmine groups

Time to rescue analgesia was significantly longer in the ketamine group (447.70± 48.109 minutes) than in the neostigmine group (257.60± 47.243 minutes) with P value ≤ 0.000. (Figure 2)

Figure 2: Time to rescue analgesia in ketamine and neostigmine groups.

Testing the correlation between time to rescue analgesia and VAS in each group; there was highly significant negative correlation at all times in the ketamine group (P value ≤ 0.005 and there was a negative significant correlation at 4, 8 and 12 hours (P value ≤ 0.05) but a negative non-significant correlation at 16, 20 and 24 hours (P value ≥ 0.05) in the neostigmine group. There was a significant difference in the analgesic dose requirement of ketrolac between ketamine (44.2±11.43 mg) group and neostigmine group (67.8±14.77 mg) P value ≤ 0.01. (Figure 3)
Ramsay score showed a non significant difference between the ketamine group and the neostigmine group at 4th, 8th, 12th, 16th, 20th and 24th hour intervals. (Figure 4)

No adverse effects observed in ketamine group but in neostigmine group One patient had shivering and one patient had bradycardia and five patients experienced postoperative nausea and vomiting but did not require treatment. No patients of the ketamine group and the neostigmine group experienced drowsiness or hypotension. (Table 2)

### Table 2: comparison of side effects between ketamine and neostigmine groups

<table>
<thead>
<tr>
<th>Group</th>
<th>NEOSTIGMINE</th>
<th>KETAMINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shivering</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>5 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Figure 3: Analgesic dose in the ketamine and neostigmine groups.

Figure 4: Ramsay score at different times of measurement in the ketamine and neostigmine groups.
DISCUSSION
Post operative pain after arthroscopic knee surgery is one of the causes of delayed discharge and rehabilitation and different ways used in management of this pain and intra-articular injection of variable drugs used for this purpose (1, 4, 5). In our study we compared between intra-articular ketamine+ bupivacaine and neostigmine +bupivacaine for postoperative analgesia in arthroscopic knee surgery, ketamine group was superior than neostigmine group in the time of analgesia and postoperative analgesic requirement,with no side effects opserved in ketamine group. Bupivacaine was used I.A due to its longer analgesic efeect .(13) the use of compined agents increased progressivaly(14, 15) to decrease the sid efects of high doses of one drug if used alone.(16) Ketamine used in pain relief because it has morphine spairing efeect ,and interact with N-methyl-D-aspartate(NMDAr) which located in the pain path way(somatic and peripheral).(17) Dal et al. studied the efeect of IA 0.5 mg/kg ketamine, I.A0.5 mg neostigmine and I.Abupivacaine 0.5% and concluded that prolnged time of analgesia and decrease opioid requirement postoperative in the three groups ,and recognized also that ketamine has long time of analgesia as neostigmine but bupivacaine has longer time.(3) Batra et al.studied 1 mg/kg ketamine alon and in compination with0.25% bupivacaine and concluded thatcombination of ketamine bupivcaine has better analgesic efeect 5.1 +/- 1.1hrs) than ketamine alone (1.7 +/- 0.9 hrs). (2) Borner et al.observed that 0.25 mg/kg ketamine decreased postoperative pain and the analgesic requirement(18)

Neostigmine used intra-articularly for pain managment after arthroscopic knee surgery .(8, 9, 19) Yang et al.compared multible neostigmen doses and concluded that I.A neostigmen 500ug was superior than 125and 250 in time of analgesia with no decrease in the suplmenyral analgesia.(8) Lauretti et al. in his study compared I.A 500ug and epidural 1ug neostigmine and concluded that epidural neostigmine in this small dose has the same analgesic efeect as I.A rout so epidural rout was effective but it is invasive procedure unless it used for anasthetic mangment.(9) Alagol et al.concluded that I.A neostigmen 500ug was the most efective drug for analgesia after arthroscopic knee surgery associated with decrease of the need of suplmentery analgesi in comparison with,clonidine, tenoxicam, morphine and bupivacaine .(5) Datta et al.observed that I.A neostigmen 500ug alone or in compination with 0.25 mg bupivicaine decrease the need osuplmental opioid and the addation of bupivacain wasnot signifinantly prolonge the duration of analgesia.(20) in our study we found the duation of analgesia in neostigmine group was 4.5 hours and in Yang , Lauretti and Datta studies(8, 9, 20) was 5 hours and inAlagol et al was 8 hours.(5)

CONCLUSION
Injection of intra-articular ketamine bupivacaine provided better postoperative analgesia, no side effects and lower supplementary analgesia than intraarticular neostigmine bupivacaine. Future studies are needed to explore the possibility of systemic absorption of ketamine through measuring the serum level and kinetics of the drug after intraarticular administration.

AUTHORS CONTRIBUTIONS
All the three authors participate in the design of this research, pre-operative patient visit, data collection, statistical analysis, interpretation of the results and writing the research article.

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DECLARATION OF INTERESTS
“The authors declare that they have no competing interests”.

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REFERENCES


