

## **Transdermal Nitroglycerin Enhances Lidocaine And Neostigmine for Intravenous Anesthesia in Patients Undergoing Hand Surgery. A Prospective Randomized Double Blind Placebo Control Study.**

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### **Abstract**

In a prospective randomized blind study, we investigated the effects of adding transdermal nitroglycerine for lidocaine and neostigmine for intravenous regional anesthesia in adult patients undergoing hand surgery.

### **Patients and Methods**

Sixty patients (ASA grade I, aged 20-60 years) of both sexes were enrolled. The patients were randomly allocated to receive either 40ml of 0.5% lidocaine plus a transdermal placebo patch (control group n=15), 40ml of 0.5% lidocaine with 0.5mg of neostigmine plus a transdermal placebo patch (Neostigmine group, n=15), 40ml of 0.8% lidocaine plus a transdermal nitroglycerine patch (Nitroglycerine group, n=15) or 40ml of 0.5% lidocaine with 0.5mg of neostigmine plus a transdermal nitroglycerine patch (Neostigmine - Nitroglycerine group, n=15). All routine hemodynamic parameters and O<sub>2</sub> saturation were monitored, surgical time, sensory and motor block onset times, sensory and motor block recovery times and time to first analgesic requirement were measured. Operative conditions and quality of anesthesia were also recorded.

### **Results**

Sensory and motor block onset times were shorter in the neostigmine – nitroglycerine group compared with all other groups (p<0.05). Sensory block recovery time was significantly prolonged and the quality of anesthesia was better in the neostigmine – nitroglycerine group compared with all other groups (p<0.05).

### **Conclusion**

We found that the addition of 0.5mg neostigmine to 40ml of 0.5% lidocaine for intravenous regional anesthesia with a 5mg transdermal nitroglycerine patch improved the operating conditions and quality of anesthesia and prolonged postoperative relief with no adverse effects.

### **Introduction**

**Intravenous** regional anesthesia (IVRA) is a technically simple and reliable form of regional anesthesia for short procedures on the extremities, with success rates of 94 – 98% <sup>(3)</sup>. It is also associated with a more favorable patient recovery profile than general anesthesia <sup>(4)</sup>. However, it has been limited by tourniquet pain, delayed onset of action, poor muscle relaxation, inability

provide post – operative analgesia, and lack of bloodless field <sup>(8)</sup>. These limitations might be avoided by the addition of various adjuncts to the local anesthetics including morphine, fentanyl, sufentanil, clonidine, atracurium, neostigmine and nonsteroidal anti – inflammatory drugs <sup>(6)</sup>.

Previously, an interest had focused on the cholinergic system that modulates pain perception and transmission. It was shown that the spinal or epidural administration of

the acetylcholine esterase inhibitor neostigmine results in a dose dependent analgesia by inhibition of the breakdown of acetylcholine (ACH) in the spinal cord <sup>(13)</sup>. There are ACH receptors in the peripheral nerves <sup>(7)</sup>, and when neostigmine was added as an adjunct to prilocaine during IVRA, the quality of anesthesia was improved, with prolonged post operative analgesia <sup>(19)</sup>. Data from the literature suggest that in human, high dose nitroglycerine are hyperalgesic, whereas doses less than 6mg per day are analgesic under different circumstances <sup>(13)</sup>. Moreover, transdermal nitroglycerine was found to enhance spinal sufentanil post operative analgesia following orthopedic surgery <sup>(16)</sup>, and it prolonged the analgesic effect of intrathecal neostigmine <sup>(13)</sup>.

The aim of the study was to determine the possible clinical advantage of application of transdermal nitroglycerine patch in patients undergoing hand surgery with IVRA using a combination of lidocaine and neostigmine.

## Patients and Methods

This study took place in King Abdulaziz Naval Base Hospital, Jubail, KSA from November 2008 to January 2010. The study was approved by the Hospital ethics Committee. After obtaining written informed consent, 60 ASA physical status I adult patients aged between 20-60 years, of both sexes, undergoing hand surgery were enrolled. Patients who were scheduled to undergo surgery that was anticipated to last more than 90 min., those with Raynaud's disease, sickle cell anemia, the use of analgesics within the last 24 hours before the study, or history of allergy to any drug used, were excluded from participation.

All patients were premedicated with 0.07mg kg<sup>-1</sup> of midazolam and 0.01mg kg<sup>-1</sup> atropine given intramuscularly 45 min. before the surgical procedure. A transdermal therapeutic system (transdermal patch) was applied to all patients at the ventral side of the upper forearm; 2 hours before the start of IVRA, and containing either nitroglycerine 5mg (a

nitric oxide generator) or a placebo according to the assigned group.

A standard technique was used in all patients. A 20-gauge cannula was inserted in a vein on the dorsum of the operative hand. Another cannula was inserted in a vein on the other arm. Patients were monitored for mean arterial blood pressure (MAP), oxygen saturation (SPO<sub>2</sub>) and heart rate (HR) in the operating room. A padded tourniquet positioned around the upper arm. The injured arm was elevated for 2 min. then exanguinated using an Esmarch band which was wrapped around the whole limb distal to the upper arm tourniquet except the hand region. The tourniquet was then inflated to 100mmHg above the patient's systolic blood pressure, and the Esmarch band was removed. Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry tracing in the ipsilateral index finger, then the local anesthetic solution was injected over 2 min.

A second tourniquet was then positioned and inflated on the anesthetized part of the arm, followed by removal of the original one.

The patients were randomized to 4 groups with 15 patients each:

**Group 1:** Receiving 40ml of 0.5% lidocaine plus a transdermal placebo patch (control group).

**Group 2:** Receiving 40ml of 0.5% lidocaine with 0.5mg of neostigmine plus a transdermal placebo patch (Neostigmine group).

**Group 3:** Receiving 40ml of 0.5% lidocaine plus a transdermal nitroglycerine patch (Nitroglycerine group).

**Group 4:** Receiving 40ml of 0.5% lidocaine with 0.5mg of neostigmine plus a transdermal nitroglycerine patch (Neostigmine – Nitroglycerine group).

A randomization list was generated and identical syringes and transdermal patches were prepared by an assistant not involved in the study. The surgeon was unaware of the group to which the patient had been allocated.

Onset of sensory block was tested by the surgeon using the pinprick method at 3 separate areas, representing the dermatomal

sensory distribution of the 3 main nerves of the hand, and anesthesia was declared when there was no sensation. Complete motor block was recorded when no voluntary movement of the fingers was possible. The sensory and motor block onset times were noted as the time elapsed from injection of the study drug to complete sensory and motor blocks respectively. The time between the start and the end of surgery (surgical time) was also noted. MAP, HR, SPO<sub>2</sub> were monitored before and after tourniquet application, 5, 10, 15, 20, and 40 min after the injection of anesthetic solution, and after release of the tourniquet by an anesthesia resident who did not know the medication given.

During surgery, the surgeon assessed the degree of muscle relaxation, the ease of reduction and the dryness of the operative field. This was on

a 0 – 10cm visual analogue scale (VAS); where the zero point indicates none, and the 10 indicates good operative conditions. At the end of operation, the anesthetist was asked to qualify the anesthetic conditions. At the end of operation, the anesthetist was asked to qualify the anesthetic conditions according to the following scale:

**Excellent (4)** = **no** complaint from the patient.

**Good (3)** = **minor** complaint with no need for supplemental analgesics.

**Moderate (2)** = **complaint** which required supplemental analgesics.

**Unsuccessful (1)** = General anesthesia was given.

Deflation of the tourniquet was performed by cyclic deflation technique (not before 30 min had been elapsed from injection of the anesthetic solution) and the transdermal patch was removed 2 h later. Sensory recovery time was noted (time elapsed after tourniquet deflation, up to recovery of pain in all dermatomes determined by pin prick test). Motor block recovery time was also noted (the time elapsed after tourniquet deflation up to movement of the fingers).

The patients were free to request rescue analgesics after tourniquet deflation and the first analgesic requirement time was noted (the time elapsed after tourniquet release to the first patient request for analgesics). An

anesthesia resident (not involved in the study) was always available to administer the analgesic (ketorolac 30mg IM.) when it was requested and pain was assessed by VAS at the time of first analgesic requirement. The patients were also monitored for the occurrence of unwanted effects as nausea, vomiting, bradycardia, central venous system side effects or skin rash after the release of tourniquet and up to 24 h postoperative in the ward and a suitable management was carried out if necessary.

Statistical analysis was performed using student's t test and chi-square test. P value < 0.05 was considered significant.

## Results

All 60 patients completed the study. There were no significant differences in patients characteristic (table1). The surgical time was similar in the 4 groups indicating similar operative conditions. Sensory and motor block onset times were statistically shorter in the neostigmine – nitroglycerine group compared with all the other groups ( $p < 0.05$ ), and they were shorter in the neostigmine group compared with the control group ( $p < 0.05$ ). Patients in the neostigmine – nitroglycerine group had a significantly prolonged sensory block recovery time compared with all other groups ( $p < 0.05$ ). The motor block recovery time was similar in the neostigmine and the neostigmine – nitroglycerine groups ( $p > 0.05$ ), but it was prolonged in these 2 groups compared to the control group ( $p < 0.05$ ) (table 2).

The VAS values of the operative conditions; assessed by the surgeon, were similar in the neostigmine and the neostigmine – nitroglycerine groups and these were statistically better in those groups compared to the control group. The quality of anesthesia determined by the anesthesiologist was significantly better in the neostigmine – nitroglycerine group compared to all other groups ( $p < 0.005$ ) (table 3). Three patients from the control group, one patient from the neostigmine

group and another two patients in the nitroglycerine group believed that they received poor anesthesia. Midazolam (2.5-5mg) and propofol (50-100mg) were used for sedation as required. These results however, were statistically insignificant.

There was no statistical difference between groups when compared for MAP, SPO<sub>2</sub> and HR at any time of measurement ( $p>0.05$ ). The first analgesic requirement time was longer for the neostigmine – nitroglycerine group compared with all other groups ( $p<0.005$ ), and it was longer

for the neostigmine group compared with the control group ( $p<0.05$ ). The pain VAS at the time of first rescue analgesic medication was similar among the 4 groups (table 4).

No significant adverse effects were seen in this study either intraoperatively or throughout the 24h postoperative period in any group, although 2 patients in the nitroglycerine group and only one patient in the neostigmine group had nausea that required treatment, but this did not reach statistical significance ( $p>0.05$ ).

**Table (1): patients' characteristics.**

	Control Group (n=15)	Nitroglycerine Group (n=15)	Neostigmine Group (n=15)	Neostigmine Nitroglycerine Group (n=15)
Age (yrs)	37(20.3)	28(13.7)	42(22.3)	39(17.7)
Sex (M:F)	8:7	7:8	9:6	8:7
Weight (Kg)	67(13.2)	65(11.4)	77(17.5)	69(16.7)
Height (cm)	168(10.3)	164(10.8)	173(8.7)	166(11.2)

Data are meaning (SD)

**Table (2): Surgical time, onset and recovery times of sensory and motor blocks (min).**

	Control Group (n=15)	Nitroglycerine Group (n=15)	Neostigmine Group (n=15)	Neostigmine Nitroglycerine Group (n=15)
Surgical Time	46(13.7)	40(8.9)	44(9.3)	41(8.7)
Sensory Block Onset Time	10.5(1.7)	10(2.1)	4.5(2.3)*	2(1.8) <sup>+</sup>
Sensory Block Recovery Time	9(1)	6(1)	18(2)*	45(3.3) <sup>+</sup>
Motor Block Onset Time	13(2)	14(1)	5(2)*	3(2) <sup>+</sup>
Motor Block Recovery Time	6(1)	3(1)	21(2)*	24(2)*

Values are mean (SD)

\* $p<0.05$  when compared with control group.

<sup>+</sup> $p<0.05$  when compared with all groups.

**Table (3): VAS for operative conditions and the quality of anesthesia.**

		Control Group (n=15)	Nitroglycerine Group (n=15)	Neostigmine Group (n=15)	Neostigmine Nitroglycerine Group (n=15)
VAS of Operative Condition		4(0-7)	3.5(0-7)	7.5(4-10)*	9(4-10)*
Quality of Anesthesia		3(2-4)	3(2-4)	3(2-4)	4(3-4) <sup>+</sup>

Values are mean (Range)

p<0.05 when compared with the control group.

+p<0.05 when compared with all groups.

**Table (4): Time to first analgesic requirement (min)**

	Control Group (n=15)	Nitroglycerine Group (n=15)	Neostigmine Group (n=15)	Neostigmine Nitroglycerine Group (n=15)
Time to First Analgesic Requirement (min)	22(7-80)	20(2-56)	49(15-130)*	106(26-210) <sup>+</sup>
VAS at First Analgesic Requirement	4.2(4-10)	4.7(4-9)	4.3(4-9)	4(4-8)

Values are median (Range)

\*p<0.05 when compared with the control group

+p<0.05 when compared with all groups.

## Discussion

The results indicate that the addition of 0.5mg neostigmine to 40ml of 0.5% lidocaine for IVRA, plus a 5mg transdermal nitroglycerine patch improved the operating conditions and the quality of anesthesia, and prolonged the time to first analgesic requirement. Our results are similar to previous studies that demonstrated the peripheral analgesic effect of neostigmine. Turan *et al*, had found that the addition of neostigmine to prilocaine in IVRA, shortened sensory and motor block onset times and prolonged the time to first analgesic requirement <sup>(19)</sup>. Yang *et al* concluded the intra-articular injection of neostigmine after knee arthroscopy produced a significant analgesic effect <sup>(24)</sup>.

Existing ACH receptors in peripheral nerves are responsible for the action of neostigmine in peripheral analgesia, and ACH plays a role in the sensory regulatory mechanisms controlled by the motor system <sup>(5)</sup>. Moreover, Varas *et al* had demonstrated the presence of ACH receptors in the soma of many petrosal ganglion neurons, thus supporting the idea that under normal conditions, peripheral sensory processes may be associated with ACH <sup>(12)</sup>.

Our results also showed that 5mg transdermal nitroglycerine patch (which releases approximately 250 micrograms of nitroglycerine per hour) alone did not result in postoperative analgesia, but the transdermal nitroglycerine patch enhanced the neostigmine analgesic effect. Their

combination resulted in improved operative conditions with better quality of anesthesia and prolonged postoperative analgesia. The transdermal patch was applied on the operative arm 2 h before the start of IVRA as the plasma concentration of nitroglycerine reaches a plateau within 2 h and maintained all through the application period<sup>(9)</sup>.

How nitroglycerine would enhance neostigmine analgesic effect is not known, and some explanations are possible. Several studies had demonstrated the synergistic interaction between nitroglycerine and the mu-opioid receptor agonists. Nitroglycerine was found to enhance morphine after intravenous or spinal administration<sup>(23)</sup>. In addition, systemic morphine increased spinal cord nitric oxide metabolite concentrations, and behavioral analgesia in healthy animals from systemic morphine is blocked by nitric oxide synthetase inhibitors<sup>(2)</sup>. Thus, because of the similarities in the different pain – modulating systems (opioid,  $\alpha 2$  adrenergic and cholinergic receptors)<sup>(22)</sup>, we could assume a similar synergistic interaction between nitroglycerine and the muscarinic agents peripherally, nitric oxide produces neither nociceptive nor antinociceptive effects on the receptors<sup>(17)</sup>. However, it modulates the anti – inflammatory process and edema formation. Its vasodilator action on the venous system decreases the vasoconstrictor tone induced by the inflammatory process and further reduces the edema formation<sup>(2)</sup>.

Finally, nitroglycerine may have an analgesic effect through the direct stimulation of peripheral fibers mimicking the actions of locally applied ACH<sup>(7)</sup>.

Therefore, the most probable explanation of our findings is the administration of the acetylcholine esterase inhibitor neostigmine might cause an analgesic effect by increasing endogenous ACH levels at the peripheral nociceptors. Because of its chemical structure, neostigmine might display longer stability<sup>(24)</sup>, there by insuring a longer analgesic effect. Thus it might enhance the availability of more

ACH at the assumed peripherally distributed ACH receptors.

Putative mechanisms of a peripheral cholinergic – mediated antinociception at the peripheral nerve endings are the hyperpolarization of neurons<sup>(20)</sup>, the reduction of pronociceptive neurotransmitter, and the activation of the nitric oxide-cyclic guanosine monophosphate (GMP) pathway<sup>(11)</sup>. In addition, Durate *et al* previously demonstrated that ACH induces analgesia via increasing cyclic GMP by generation of nitric oxide<sup>(7)</sup>. Therefore, application of transdermal nitroglycerine patch (a nitric oxide donor) could enhance the neostigmine analgesic effect.

No adverse effects were seen in this study. No evidence of central nervous system side effects or cardiac arrhythmias was seen after local anesthetic administration, before and during surgery and after release of the tourniquet. This could be due to the relatively long operative time in all patients (more than 40 min) and the deflation of tourniquet by the cyclic deflation technique. The small dose of neostigmine used and the patient's premedication with atropine may have a role in preventing unwanted neostigmine effects.

In conclusion, we found that the addition of 0.5mg neostigmine to 40ml of 0.5% lidocaine for IVRA with a 5mg transdermal nitroglycerine patch, improved the operating conditions and quality of anesthesia, and prolonged postoperative pain relief, with no adverse effects. Therefore, this technique is worth further investigations to determine the effect in different peripheral blocks.

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## إعطاء النيتروجلسرين عن طريق لصقه جلديه يعزز تأثير التخدير الموضعي الوريدي بواسطة الليدوكيين و النيوستجمين عند البالغين الخاضعين لجراحة اليد

دراسة عشوائية

د/ اسامه فاروق, د/ جمال شاهين, د/ حسن ابو دله, د/ محمد عبد القوى, و د/ عمرو مختار

من خلال دراسته عشوائية في مستشفى قاعدة الملك عبد العزيز البحرية, الجبيل, المملكة العربية السعودية, تم اكتشاف تأثير إضافة النيتروجلسرين عن طريق لصقه جلديه على استعمال الليدوكيين و النيوستجمين كمخدر موضعي عند البالغين الخاضعين لجراحة اليد.

تم أخذ عينه من البالغين تتراوح أعمارهم بين ٢٠ - ٦٠ سنة و تصنيفهم بالدرجة الأولى حسب الجمعيه الأمريكيه للتخدير و تقسيمهم الى ٤ مجموعات.

**المجموعه الأولى** أعطيت ٤٠ مللتر من الليدوكيين بتركيز ٠,٥٪ مع لصقه جلديه وهميه.

**المجموعه الثانيه** أعطيت ٤٠ مللتر من الليدوكيين بتركيز ٠,٥٪ و نصف ملجرام نيوستجمين مع لصقه جلديه وهميه.

**المجموعه الثالثه** أعطيت ٤٠ مللتر من الليدوكيين بتركيز ٠,٨٪ مع لصقه جلديه من النيتروجلسرين.

**المجموعه الرابعه** أعطيت ٤٠ مللتر من الليدوكيين بتركيز ٠,٥٪ و نصف ملجرام نيوستجمين مع لصقه جلديه من النيتروجلسرين.

و تم مراقبة العلامات الحيويه و نسبة تشبع الدم بالأكسجين مع تسجيل مدة الجراحه, بداية توقف الحركة و الإحساس باليد و عودة الحركة و الإحساس باليد و كذلك توقيت بداية إحتياج المريض لمضادات الألم بعد العمليه وكذلك مدى جودة التخدير أثناء العمليه.

تبين من خلال الدراسة أن بديه فقدان الحركة و الإحساس باليد (التخدير) كان اسرع و عودة الاحساس بعد فتره أطول و كفاءة التخدير في المجموعه الرابعه.

في النهايه تبين ان إضافة نصف ملجرام نيوستجمين الى ٤٠ مللتر من الليدوكيين بتركيز ٠,٥٪ للتخدير الموضعي مع ٥ ملجرام لصقه جلديه من النيتروجلسرين حسنت ظروف الجراحه و جودة التخدير و اطالت فترة الإحتياج لمضادات الألم بعد العمليه و بدون آثار جانبيه.