EFFICACY OF NITROGLYCERINE AS AN ADJUVANT TO INTRAVENOUS REGIONAL ANESTHESIA: A REVIEW OF LITERATURE

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IMPLICATION STATEMENT:

Various adjuvants like opioids, alpha-2 agonists, steroids and many more drugs have been mixed with local anaesthetic (LA) solutions for Intravenous Regional Anaesthesia (IVRA). These drugs are added with the aim of hastening the onset of action and prolonging the duration of analgesia. They may also allow for a reduction in the total dose of LA used and related side effects. In this article, we have reviewed clinical trials using nitroglycerine (NTG) as an adjuvant to LA in IVRA and have summarized the advantages, disadvantages and current role of this drug. To the best of our knowledge, no meta-analysis, or review article has analysed the role of NTG as an adjuvant to Bier's block.

Keywords: *Intravenous regional anaesthesia, Nitroglycerine, VAS score, Adjuvants for Bier's block.*

INTRODUCTION

Intravenous regional anaesthesia (IVRA) is a suitable technique for short duration surgeries lasting for less than an hour and involving the upper and lower limbs below the elbow and knee joints respectively.[1] Various adjuvants like opioids, alpha-2 agonists, steroids, ketamine, non-steroidal anti-inflammatory drugs and many more drugs have been mixed with local anaesthetics (LAs) for IVRA.[2-5] These drugs are added with the aim of hastening the onset of action and prolonging the duration of analgesia. They may also allow for a reduction in the total dose of LA used and related side effects. Nitroglycerine (NTG) when used as an adjuvant promotes distribution of lignocaine to nerve endings and thereby prolongs the duration of its action. In the present review we analyzed clinical trials using NTG as an adjuvant to LA for IVRA and summarized its current role, advantages and disadvantages.

METHODOLOGY

A thorough and comprehensive literature search in medical databases (PubMed, Google Scholar, and Ovid MEDLINE) was performed with stepwise changes in relevant keywords (IVRA, nitroglycerine, local anaesthetics and adjuvants for Bier's block) without any data restriction including case reports, observational studies, randomised controlled trials (RCTs), and review articles. However, all the evidences that we found in the literature was in the form of RCTs. Nevertheless, as a result of the extremely broad spectrum of publications, unintentional bias caused by omission of potentially relevant articles cannot be fully excluded.

BIER'S BLOCK

IVRA is a suitable technique for short duration surgeries generally lasting for less than an hour and involving procedures on the upper and lower limbs below the elbow and knee joints respectively. It is also known as Bier's block after the founder August Bier, who first described this technique in the year 1908 for anaesthetizing the hand and forearm. [1] However the main disadvantages of this technique include slow onset of action, poor muscle relaxation, pain at tourniquet site, minimal postoperative pain relief and the potential systemic toxicity of the LA agent. (6) Various adjuvants have been added to the solution of LA including opioids, non-steroidal anti-inflammatory drugs, alpha-2 agonist (clonidine, dexmedetomidine), dexamethasone, sodium bicarbonate to minimize these limitations of IVRA.(2-5) A few RCTs[7-12] have reported that using NTG as an additive to LA solution in IVRA improves onset of action decrease pain at tourniquet site resulting in an improvement in the overall quality of the block and reduction in the perioperative analgesic consumption.

MECHANISM OF ACTION OF NTG

The exact mechanism of action of IVRA is not clearly known. However, there appear to be multiple complementary mechanisms producing analgesia and anaesthesia. The effect of LA agents on nerve endings, tissue ischemia, asphyxia, hypothermia, and acidosis play an important role. [13] In addition to all these effects, the strong vasodilatory effect of NTG may promote distribution of lignocaine to nerve endings improving the efficacy of block. [14] NTG is metabolized to nitric oxide (NO) which causes an increase in the intracellular concentration of cyclic

guanosine monophosphate (cGMP), which generates pain modulation in the central and peripheral nervous system.[15] Activation of NO-cGMP signal transduction system causes sensitization of wide dynamic-range neurons located in the superficial and deep dorsal horns of the spinal cord and concurrently attenuates pain signal transmission. [16]

REVIEW OF LITERATURE

In a RCT, Sen et al [7] evaluated the analgesic effects of NTG when added to lignocaine in IVRA. Thirty patients undergoing hand surgery were randomly assigned to two groups. The control group (n=15) received a total dose of 40ml of lignocaine (3mg/kg) diluted with saline, and the NTG group (n=15) received an additional 200µg of NTG. Hemodynamic variables, tourniquet pain and analgesic consumption were compared between the two groups. The authors found statistically significant shortened onset of sensory (4.5 ± 1.2 vs. 3.2 ± 1.1 min) and motor blockades (3.3 ± 1.6 vs. 5.2 ± 1.8 min), prolongation of sensory and motor blockade by (3.1 ± 1.2 vs. 6.8 ± 1.6) and (3.6 ± 0.8 vs. 7.3 ± 1.3 min) respectively. Improved quality of anaesthesia as determined by the patient's and the surgeon's satisfaction score were also observed. Visual analogue scale (VAS) scores after the tourniquet release and in the postoperative period were lower in the NTG group. Time to first rescue analgesic requirement was also longer in the NTG group (225 ± 74 min vs. 39 ± 33 min) as compared to control group. One patient in control group and two patients in NTG group developed headache post-operatively, which was statistically non-significant and got resolved by its own.

Elmetwaly and colleagues [8] compared the effects of adding either ketamine or NTG as adjuncts to lignocaine for IVRA on intraoperative and postoperative analgesia, sensory and motor block onset times, and tourniquet pain. Seventy-five patients undergoing hand surgery were prospectively divided into three groups: L group receiving lignocaine 2% alone, or to LK group receiving lignocaine 2% and ketamine 0.1 mg/kg, or to LN group receiving lignocaine2% and NTG 200 µg. Sensory block onset times were shorter in the LK (4.4 ± 1.2 minutes) and LN (3.5 ± 0.9 minutes) groups compared with the L group (6.5 ± 1.1 minute) (P <0.0001) and motor block onset times were shorter in the LK (7.3 ± 1.6 minutes) and LN (3.6 ± 1.2 minutes) groups compared with the L group (10.2 ± 1.5 minutes) (P<0.0001). Sensory recovery time got prolonged in the LK (6.7 ± 1.3 minutes) and LN (6.9 ± 1.1 minutes) groups compared with the L group (5.3 ± 1.4 minutes). Motor recovery time also got prolonged in the LK (8.4 ± 1.4 minutes) and LN (7.9 ± 1.1 minutes) groups compared with the L group (7.1 ± 1.3 minutes). The amount of rescue analgesic in the form of fentanyl required for tourniquet pain was less in adjuvant groups when compared with control group (13.6 ± 27.9 vs. 27.6 ± 34.9 vs. 54.8 ± 28 µg respectively). VAS scores of tourniquet pain were higher at 10, 20, 30, 40 minutes in the control group compared with the two study groups. The authors concluded that adjuvant drugs (ketamine or NTG) when added to lignocaine in IVRA were effective in improving the overall quality of anesthesia, reducing tourniquet pain, increasing tourniquet tolerance and improving the postoperative analgesia in comparison to the control group. NTG as an adjuvant produced faster onset of sensory and motor blockades in comparison to other groups.

Effects of NTG in quality improvement when added to lignocaine in IVRA were evaluated by Barazandeh et al.[9] Authors enrolled 40 patients and randomly allocated them into two groups. Control group received 3mg/kg of 0.5% lignocaine alone and the study group received 200µg of NTG in addition to similar dose of lignocaine. Hemodynamic variables, onset and recovery times of sensory and motor blockades, and tourniquet pain based on VAS score were recorded in all patients. Sensory block onset time was shortened in the study group compared to the control group (2.45 ± 0.51 vs. 4.35 ± 1.26 min). Sensory (8.25 ± 2.17 vs. 3.82 ± 0.99 min) and motor (4.2 ± 1.15 vs. 3.02 ± 0.8 min) recovery times following tourniquet deflation were prolonged in the study group compared to the control group. The onset time to tourniquet pain was prolonged in the study group compared with the control group (22.5 ± 3.12 vs. 19.4 ± 2.77 min). In addition the pulse rate at 0.5, 2 and 4 hours post-operatively was significantly lower in the study group as compared to control group(P<0.05).

In a double-blind RCT, Abbasivash et al [10] evaluated the effect of NTG in quality improvement when added to lignocaine in IVRA. Forty-six patients were randomly allocated to either of two groups: control group received 3mg/kg of 1% lidocaine diluted with saline, and the study group receiving an additional 200µg of NTG. Onset of sensory and motor block were shortened in the study group (2.61 vs. 5.09 and 4.22 vs. 7.04 min, respectively) (p <0.05). The recovery time of sensory and motor block and onset of tourniquet pain were also prolonged in the study group (7.26 vs. 3.43, 9.70 vs. 3.74 and 25 vs. 16.65 min respectively) (p <0.05). Intra-operative rescue analgesics required in the form of fentanyl and pethidine during first postoperative day and pain intensity at 4, 6, 12 and 24 hours postoperatively were lower in the study group (p <0.05). The authors concluded that addition of NTG to lignocaine in IVRA improved the quality of blockade, decreased tourniquet pain and opioid consumption on the first post-operative day.

Asadil HK et al[12] evaluated the effect of NTG on sensory and motor block onset and recovery

time as well as the quality of tourniquet pain relief, when added to lignocaine for IVRA in patients undergoing elective forearm and hand surgery. Similar to the results of other RCTs, the authors found shortened onset times of sensory (2.94 ± 1.02 vs. 6.30 ± 2.46 min) and motor blockade (9.69 ± 1.02 vs. 13 ± 5.28 min), prolonged recovery from sensory (10.69 ± 3.97 vs 7.18 ± 2.41 min) and motor blockade (8.41 ± 7.17 vs. 8.33 ± 3.27 min) and improved quality of anaesthesia. However, there was no difference in the mean pain score over time between the two groups.

We found only one RCT in literature where in the authors evaluated the analgesic effect of three different doses of NTG (200µg, 300µg and 400µg) used as an adjuvant to lignocaine for IVRA. [11] A Hundred patients undergoing hand surgery were randomly allocated to four groups to receive 3 mg/kg of 2% lignocaine diluted with saline to a total dose of 40ml in the control group (Group LS, n=25) or an additional of 200, 300, 400µg NTG in the study groups (Groups LN1, LN2, LN3 respectively; n=25 in each group). Sensory and motor block onset times were significantly shorter in group LN3 compared with groups LN1, LN2, and LS ($p<0.05$). Sensory and motor block recovery times were also statistically prolonged in group LN3 when compared with groups LN1, LN2 and LS ($p<0.05$). Similarly, post-operative VAS scores were significantly lower at 2, 4, 8, 12, and 24 hours after tourniquet release in group LN3 compared with group LS ($p<0.05$). Hence, addition of 400µg of NTG was found to be superior to 200µg or 300µg, without causing side effects. Only one patient in group LN2, three patients in control group and similar number of patients in group LN3 developed hypotension intra-operatively requiring fluid and vasopressor boluses. Tachycardia (increase in heart rate more than 30% of baseline) was noted in one patient per group in LN3 and LN2. Two patients in group LN1 developed hypertension which was transient and required no active interventions. Two patients in control group complained of postoperative nausea whereas no patient in any of the study groups had either nausea or vomiting. However none of these finding were statistically significant.

CONCLUSION

Addition of NTG as an adjuvant to lignocaine (in a dose of 200 µg) for IVRA shortened the onset of sensory and motor blockade, improved overall quality of anaesthesia; prolonged the duration of sensory and motor blockade recovery times, improved tolerance of tourniquet pain, increased the time to first rescue analgesic requirement, and decreased post-operative opioid consumption without producing any significant side effects and hemodynamic instability. The decrease in the amount of intraoperative and postoperative opioid consumption as well as the time to first rescue analgesic requirement observed in a few RCTs was statistically and clinically significant. However, the addition of NTG as an adjuvant to LA in IVRA hastened the onset and prolonged the duration of sensory and motor blockade recovery times by only 3 to 5 minutes. Therefore these findings are statistically significant but do not have clinical importance and utility.

Due to the availability of ultrasonography at many of the centers practicing regional anesthesia as well as due to the availability of safe and effective adjuvants like opioids and alpha-2 agonists, the use of IVRA and NTG as an adjuvant to LA for IVRA are on the decline. However, future large scale RCTs using NTG as an adjuvant for different ultrasound guided peripheral nerve blocks may help to determine the exact role and efficacy of NTG as an adjuvant in regional anesthesia practice.

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