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Original article

The use of vitamin B1 as a perineural adjuvant to middle interscalene block for postoperative analgesia after shoulder surgery

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Summary. *Background:* Perineural administration of thiamine, via axonal flow, could strenghthen synthesis of ACh in the dorsal horn inhibitory interneurons, thus potentiating analgesia. The purpose of the present retrospective analysis is therefore to investigate whether adding perineurally 2 mg/Kg of thiamine to 0.75% levobupivacaine in patients undergoing middle interscalene block may prolong the duration of analgesia. *Method:* The hospital records of all ASA status 1-2 patients, undergoing a single-shot interscalene block for arthroscopic rotator cuff repair from January 2011 to May 2012 were retrospectively reviewed. All blocks were performed with 0.75% levobupivacaine or a solution of thiamine hydrochloride and 0.75% levobupivacaine. The local anesthetic solution, postoperative visual analogue score for pain at rest and rescue medication were registered. We calculated the time interval elapsing between block anesthetic mixture injection and the patient's first analgesic requirement, ie time to end of analgesia. Eventual postoperative side effects were also reported. *Results:* 59 patients received 0.4 ml/Kg of 0.75% levobupivacaine (Group L) and 51 patients received a mixture of 2 mg/Kg of thiamine hydrocloride (maximum dose 200 mg) with 0.4 ml/Kg of 0.75% levobupivacaine (Group B1). Tea was 11.4 ± 3.0 hours in Group L versus 17.6 ± 3.0 hours in Group B1 ($p < 0.001$). The scores for pain in the two Groups at the time of the first analgesic rescue were comparable. *Conclusion:* The present retrospective analysis suggests that thiamine helps to prolong postoperative analgesia when added to the local anesthetic solution. Further prospective studies are necessary to confirm these preliminary results. (www.actabiomedica.it)

Key words: interscalene block, postoperative analgesia, regional anesthesia, adjuvant, thiamine

Introduction

The best solution to prolong postoperative analgesia in regional anesthesia is inserting a perineural catheter, which is also important for an early start of physiotherapy (1). If surgery is carried out in a day-hospital setting, not all anesthesiologists are willing to discharge a patient with a perineural catheter still attached, because of possible infection (2, 3).

Many adjuvants have been investigated for perineural analgesia (4,5), but only buprenorphine and tramadol have achieved some results in terms of ef-

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ficacy when perineurally added to local anesthetics for postoperative analgesia (6-9), although some side effects have been reported, such as nausea and vomiting.

The neurotransmitter acetylcholine has a relevant role in pain control at the level of the dorsal horns of the spinal cord. An increased release of spinal acetylcholine is associated with an elevated pain threshold, while a decreased release is associated to hyperalgesia, as seen after systemic treatment with a muscarinic agonist and an antagonist (10). Muscarinic and nicotinic receptors are both present in the dorsal horns of the spinal cord. Postsinaptic M1 as well as presinaptic M2 muscarinic receptors have been demonstrated at this level: the latter ones, activated by inhibitory interneurons, regulate ACh release (11).

Once in the synaptic cleft, acetylcholine will be catalyzed by the enzyme acetylcholinesterase. Neostigmine, a cholinesterase inhibitor, has been therefore investigated as an adjuvant to local anesthetics. When administered intrathecally at low doses (50 mcg) it prolongs block duration, achieving longer postoperative analgesia but also prolonging motor block and therefore delaying hospital discharge in day-case surgery. Lower doses of neostigmine (6.25-12.5 mcg) do not prolong spinal anesthesia but still induce side effects, such as nausea and vomiting, tachycardia and tachypnea (12). Although some encouraging results after spinal injection, when administered as an adjuvant to the local anesthetic solution for brachial plexus block, neostigmine failed to produce any analgesic benefit, and still showed relevant side effects (13). Therefore, neostigmine does not seem to penetrate peripheral axons when administered perineurally, although its systemic absorption seems to still induce side effects.

Thiamine (vitamin B1) is a necessary compound for acetylcholine (ACh) synthesis as a co-enzyme to ACh-CoA carboxylase. Therefore we have hypothesized that administering thiamine at the perineural level could help synthesis of ACh leading to its storage at the level of presinaptic vescicoles, thus potentiating analgesia. Moreover, due to its chemical nature as a co-enzyme, thiamine shows a much longer half-life than neostigmine. We administered perineural thiamine together with a long acting local anesthetic because this latter gives the vitamine time to migrate to the posterior root ganglion and the dorsal horn of the spinal cord.

To empirically test our hypothesis, we started administering thiamine within a local anesthetic solution of 0.75% levobupivacaine for brachial plexus blocks, and observed some encouraging results. Starting from January 2011, some of the anesthesiologists in our institution started using 2 mg/Kg of thiamine as an adjuvant to perineural levobupivacaine for shoulder surgery.

The purpose of the present retrospective analysis is to investigate whether adding perineurally 2 mg/Kg of thiamine to 0.75% levobupivacaine, in patients undergoing middle interscalene block (MIB) (14) for arthroscopic rotator cuff repair, prolongs the duration of postoperative analgesia in comparison to the administration of 0.4 ml/kg of 0.75% levobupivacaine alone.

Methods

After Ethics Committee approval for chart reviewing the hospital records of all American Society of Anesthesiologist (ASA) physical status 1-2 adult patients, who had undergone a single-shot MIB for elective arthroscopic rotator cuff repair, at the Department of Anesthesia and Pain Therapy, San Camillo Hospital, Brescia, Italy from 19th of January 2011 through to 31st of May 2012, were retrospectively reviewed.

Data from intraoperative anesthesia and surgical floor records were collected by a single reviewer and recorded in a database.

Both anesthesia and surgical procedures were routinely carried out, in a standardized fashion, according to clinical protocols at our institution. All patients were sedated with 0.1 mg/kg of diazepam per os two hours before being transferred to the operating room. On arrival in the operating room, standard non-invasive monitoring (ECG, SpO_2, NIBP) and an 18-gauge venous access in the contralateral arm were established. Patients' age, weight and height were reported as usual in the anesthesia record.

All patients within the retrospective analysis received a MIB using a 24 G, 35 mm, teflon-coated needle connected to the negative lead of a nerve stimulator (2 Hz, 0.1 msec, 0.5 mA). All patients within the reviewed charts received a perineural injection of either 0.4 ml/Kg of 0.75% levobupivacaine or a local anesthetic solution of 0.4 ml/Kg of 0.75% levobupiva-

caine mixed together 2 mg/Kg thiamine hydrochloride (max 200 mg), according to the anesthesiologist's preference. The kind of local anesthetic solution, as well as doses of drugs within the solution and sensory block onset times were reported in the anaesthesia record. All MIBs were carried out by anesthesiologists with a high level of experience in regional techniques (at least 90 MIBs per year and 4 years' experience).

After surgery, patients were transferred to the orthopedic floor and monitored as usually for the duration of postoperative analgesia. All patients were instructed to call for help in case of pain and were given ketorolac 30 mg with ranitidine 50 mg and tramadol 100 mg in 100 ml of saline solution as pain rescue medication. When called by the patient for pain rescue medication, the nurse questioned him/her about his/her visual analogue score (VAS) for pain at rest. The visual analogue score (VAS) was registered as usually in the chart together with the time of the patient's request and the medication thereafter administered.

The time interval elapsing between injection of the local anesthetic solution (a time well known) and the patients' first analgesic requirement, i.e. time to end of analgesia (Tea), was considered as the indicator of analgesia duration, when performing the retrospective analysis. If a patient did not require any analgesic drug, Tea was considered 24 hours.

Eventual postoperative side effects were also reported in the chart. In case of nausea or vomiting patients were given intravenous levosulpiride 25 mg.

If some patient needed intraoperative analgesia, we administered 0.05 - 0.1 mg fentanyl If more than 0.1 mg were administered, the block was considered unsuccessful and the patient's clinical record was not included in the study.

Statistical analysis

Continuous variables were presented as mean (± SD) and were compared between the two treatment groups by means of the Student's t test. Qualitative variables were described as count and percentage and were between the two treatment groups by means of the χ^2 test or Fisher's exact test.

The statistical analysis of the duration of postoperative analgesia in the two treatment groups was carried out on the basis of the survival function (Kaplan-Meier) and the Log-rank test (Fig. 1).

The patients accrual has been stopped at about 50 patients in each treatment group when it is possible to demonstrate with a power of 0.80 an effect size of about 0.55 at a Student's t test (significance level of 0.05, two tailed) or a difference of 0.20-0.25 (about) between two proportions at a zeta test (or χ^2 with a significance level of 0.05, two tailed) or a difference of 0.20-0.30 between two survival probabilities at a Log-rank test (significance level of 0.05, two tailed).

A p value ≤ 0.05 was considered as statistically significant.

Statistical analysis was performed using the Sigmaplot 12.0 statistical software package.

Results

During the 16-month period, 59 patients undergoing single-shot MIB for arthroscopic rotator cuff repair received 0.4 ml/Kg of 0.75% levobupivacaine (Group L) and 51 patients received an anesthetic solution consisting of a mixture of 2 mg/Kg of thiamine hydrocloride (maximum dose 200 mcg) with 0.4 ml/Kg of 0.75% levobupivacaine (Group B1).

Demographic and anthropometric characteristics were comparable between groups (Table 1).

Mean (sd) Tea was 11.4 ± 3.0 hours in Group L versus 17.6 ± 3.0 hours in Group B1 (p < 0.001) (Table 2). Tea is illustrated as Kaplan-Meier survival function in Figure 1.

Table 1. Characteristics of the study population

Variable (mean +/- SD)	Group L	Group B1	p value
Age (years)	56 ± 12	58 ± 12	0.39
Height (cm)	168 ± 9	167 ± 7	0.70
Weight (Kg)	74 ± 14	72 ± 15	0.50

Table 2. Analgesia results

Variable (mean +/- SD)	Group L	Group B1	p value
Tea [mean ± SD] (hours)	11.4 ± 3.0	17.6 ± 3.0	< 0.001
Visual Analogue Score [median (range)]	4 (4-5)	5 (4-6)	0.076
Onset of sensory block [median (range)] minutes	4.7 (3.0-10.0)	4.9 (3.0-20.0)	0.7085

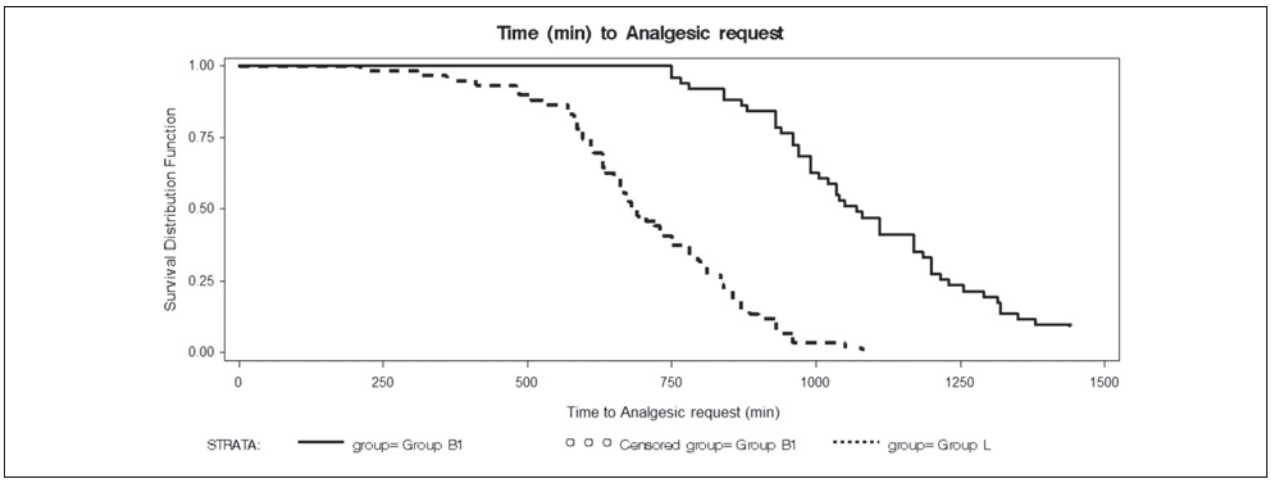

Figure 1. Kaplan-Meier curve of time to end of anesthesia, i.e. time to first analgesic request

The onset of sensory block was comparable in the two groups [4.7 (3.0-10.0) in Group L versus 4.9 (3.0-20.0) in Group B1, p = 0.7085].

The VAScores for pain in the two Groups at the time of the first analgesic rescue were similar between the two groups: 4 (4-5) in Group L versus 5 (4-6) in Group B1 (p = 0.076).

The rare cases of nausea or bradycardia were respectively resolved with levosulpiride or atropine i.v. We recorded no cases of vomiting, hypotension or dyspnea.

Discussion

The present retrospective analysis suggests that thiamine helps to prolong postoperative analgesia when added to the local anesthetic solution in patients undergoing MIB for arthroscopic rotator cuff repair: analgesia lasted 6 more hours in those patients receiving vitamin B1 as an adjuvant to levobupivacaine.

Several studies have already demonstrated antinociceptive and antihyperalgesic effects of thiamine in animal models (15,16). When systemically administered, the analgesic effects of B vitamins have been associated to various mechanisms. Some Authors postulated an increase in inhibitory control of afferent nociceptive neurons in the spinal cord (17) and a reduced response of thalamic neurons to nociceptive stimulation (18). More recently, it was demonstrated that the analgesic effects induced by B vitamins were partially blocked by naloxone, suggesting that B vitamins could indirectly activate opioid receptors (17). There is also experimental evidence suggesting that the effects of B vitamins involve the nitric oxide-cGMP system (19). Although the real mechanisms await future explanation, other positive results about the antinociceptive efficacy of thiamine and B vitamins have also been seen in some clinical trials. In particular B vitamins, including thiamine, have been used alone or in combination with NSAIDs for polyneuropathies, degenerative diseases of the spinal column, rheumatic diseases and pain after tonsillectomy (20-24). Recently, another study has demonstrated the utility of the diclofenac-B vitamins combination for treatment of acute pain following lower-limb fracture and surgery (25).

As an adjuvant to loco-regional anesthesia, vitamin B1 as been already applied many years ago, in 1947 (26-28). Two years later Lucien Leger and Monique Lande published an article about the use of vitamin B1 as an adjuvant to local and spinal anesthesia (29). In the same year Gastone Parturier in a letter to the Editor of the Presse Medicale highlighted the "Action anesthésiante de la vitamin B1" (30). Always in 1949, De Nunno published an article (31) about an experimental study on the ischiatic nerve of the rabbit, referring good results. However an odontojatric application by Magri from Padua University in 1951 (32),

was without results. But in this last study the dilution of vitamin B1 was so extreme that could be defined "homeopathic".

In the present retrospective analysis, the perineural administration of thiamine in association with levobupivacaine in patients undergoing single-shot MIB has demonstrated encouraging results in terms of prolongation of postoperative analgesia. To our knowledge, this is the first clinical observation of the potential benefits of adding thiamine to local anesthetic as perineural adjuvant. Our choice to mix vitamin B1 with a long-acting local anesthetic was made in order to have enough time for thiamine migration to the posterior horn of the spinal cord. We are however conscious that the present study presents some limitations. Besides the retrospective nature of the analysis, it would had been interesting to investigate the potential benefits of thiamine systemic administration in the same clinical context. Further prospective studies are therefore necessary to be conclusive about its efficacy as a perineural adjuvant. Nevertheless, if it were confirmed that perineural thiamine can selectively reduce nociceptive pain perception, its greatest advantage would be to prolong postoperative analgesia with minimal or no risk at all of side effects or complications, as thiamine is one of our natural co-enzymes (a vitamine) and not a foreign molecule.

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