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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Article first published online: January 4, 2019. - Manuscript accepted: December 17, 2018. - Manuscript revised: November 22, 2018. - Manuscript received: September 17, 2018.

(*Cite this article as:* Piliego C, Longo F, Costa F, Martuscelli M, Claps F, Agrò FE. Are we doing all we can for procedural pain? Evaluation of the efficacy of pectoral nerve block for port catheter positioning. Minerva Anestesiol 2019;85:560-1. DOI: 10.23736/S0375-9393.18.13308-6)

Online version at http://www.minervamedica.it
Minerva Anestesiologica 2019 May;85(5):561-2
DOI: 10.23736/S0375-9393.18.13395-5

Rapidly fatal neurological and cardiocirculatory failure in a patient recently treated with nefopam

A 65-year-old woman was found unconscious (Glasgow Coma Scale 3/15) and with respiratory failure (gasping) at the pneumology ward where she had been admitted for chronic obstructive pulmonary disease (COPD) exacerbation. She had a history of psychiatric disorders treated with several psychoactive drugs and a recent traumatic lumbar vertebral fracture requiring the introduction of analgesics. Her recent therapy included: amisulpride 50 mg/day, aripiprazole 15 mg/day, amitriptyline 75 mg/day, mirtazapine 15 mg/day, bupropion 300 mg/day, tramadol 300 mg/day. Oral nefopam was rapidly increased from 30 to 120 mg/day over two days and she received the last dose of 60 mg about five hours after the acute event. At the arrival of the medical intervention team, blood pressure was 90/40 mmHg, heart rhythm was irregular (150/min), respiratory rate <5 breaths/min, and temperature 39.2 °C. After intubation, the patient was transferred to the intensive care unit, where she was found with dilated and poorly reactive pupils, diaphoresis and generalized myoclonic jerks that were only transiently improved after diazepam administration. The EEG (diffuse slowing, 4 Hz) failed to demonstrate epileptic activity. Rectal temperature rose up to 40 °C. Further evolution was characterized by a major hemodynamic instability with variable heart rhythm 70-140 bpm, while electrocardiogram revealed supraventricular tachycardia with a *de-novo* right bundle branch block. Contractility was preserved at echocardiography. Despite cooling measures (including neuromuscular blocking agents), fluid resuscitation and infusion of massive doses of epinephrine and norepinephrine (up to 6 µg/kg/min), the patient died within six hours from refractory shock. Laboratory investigations were poorly relevant at the exception of a mild hyperlactatemia. All the psychoactive drugs were within therapeutic range. Blood cultures remained sterile. Investigation by brain and thoracic computed tomography was also negative. Post-mortem examination failed to reveal any specific lesion.

Serotonin toxicity was suspected. Classically, the recognition of the so-called serotonin syndrome (SS) is based on the triad of cognitive impairment, autonomic dysfunction and abnormalities of neuromuscular function.[1, 2] It is not unusual for signs and symptoms from only one or two of these categories to predominate. The severity of the clinical manifestations appears extremely variable and fatalities are usually related to autonomic disorders with hypotension carrying an unfavorable prognosis. In general, the onset of SS is precipitated by a change in dose of a serotoninergic drug or by the recent addition of another serotoninergic agent. In our patient, impaired cognition, hyperthermia, myoclonic jerks, diaphoresis and dysautonomia were all consistent with clinical manifestations of serotonin toxicity. Muscle rigidity is frequent in SS, but its absence does not exclude SS especially as neuromuscular blocking agents were early administered to prevent progression of hyperthermia. As serotonin syndrome is often a diagnosis of exclusion, common causes of shock (infectious, cardiogenic, etc.) have to be reasonably ruled out. The patient's chronic treatment included numerous drugs that were associated with the occurrence of serotonin syndrome, either as a single drug therapy or in combination. The only recent change was the introduction of increasing doses of nefopam. Nefopam is a non-opiate potent analgesic whose mechanism of action is not fully understood. Inhibition of catecholamines and serotonin reuptake in the central nervous system has been suggested. Specific *in-vitro* ligand studies revealed that nefopam showed various affinities for serotoninergic receptor subtypes with decreasing affinities for 5-HT_{2C}, 5-HT_{2A}, 5-HT_3, 5-HT_{1B}, and 5-HT_{1A} receptor subtypes.[3, 4] Analgesic properties appear related to its action on 5-HT_3 receptors. Few studies have investigated nefopam-induced adverse drug reactions.[5] Fatalities appear extremely rare; death seems to be related to convulsions and cardiovascular events. In the present observation, the close temporal relationship with the introduction of nefopam, points out the possible responsibility of nefopam in the fatal adverse event. Whether this could be related to serotoninergic properties of the drug remains debatable, as there are no laboratory or ancillary tests for SS. The clinicians should be aware of the risks of combining drugs with serotoninergic properties.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Article first published online: January 4, 2019. - Manuscript accepted: December 17, 2018. - Manuscript revised: November 29, 2018. - Manuscript received: October 22, 2018.

(*Cite this article as:* Trungu J, Laarbaui F, Dechamps M, Hantson P. Rapidly fatal neurological and cardiocirculatory failure in a patient recently treated with nefopam. Minerva Anestesiol 2019;85:561-2. DOI: 10.23736/S0375-9393.18.13395-5)

Online version at http://www.minervamedica.it
Minerva Anestesiologica 2019 May;85(5):562-3
DOI: 10.23736/S0375-9393.19.13476-1

The perpendicular sacral plexus block: an alternative approach to the sacral plexus

The sacral plexus block is of fundamental importance for analgesia in hip replacement surgery.

It can also be used as a substitute for spinal anesthesia, when associated with the lumbar plexus block in patients with hip fracture, in which the conventional technique can be dangerous.[1, 2] One of the most well-known approaches to the lumbar plexus is represented by the "parasacral parallel shift" (PSPS) approach.[3] This technique is extremely useful for identifying the greater sciatic foramen and the sacral plexus from which it emerges. Furthermore, it can be used to identify the piriformis muscle for antalgic techniques involved in the treatment of chronic pain.[4]

On the other hand, the technique could be hard to be performed because of the depth of the structures, both for the difficulty in visualizing them and in following the needle to the target structure. Failure to visualize the tip of the needle may result in a vascular and nervous structures damage as well as in a wrong needle entering into the pelvic cavity.[5]

With this in mind, for the identification of the sacral plexus we propose a variant of the PSPS approach: the "perpendicular sacral plexus block," that we have successfully performed in a 79-year-old, obese (BMI 39.7) woman (ASA physical status 4) with a history of coronary artery disease in dual antiplatelet therapy (clopidogrel 75 mg + acetylsalicylic acid 100 mg) and severe aortic stenosis. The patient was scheduled to undergo total hip arthroplasty (THA) for femoral neck fractures.

Considering the high anesthesiologic risk, we decided to perform a combined lumbar and sacral plexus block, as a sole anesthetic method, in order to avoid the use of general or spinal anesthesia.

Peripheral venous access was obtained and ECG, HR, SpO2, non-invasive blood pressure (NIBP) were monitored, then the patient was placed in the lateral position with the limb to be treated facing upwards. After careful skin disinfection and draping, the antalgic procedure was performed.

A convex probe (3-5 Mhz) was placed in the middle third between the iliac crest and the greater trochanter. In this way the profile of the Iliac bone, the gluteus medius muscle and the gluteus minimus muscle were visualized. Subsequently, the probe was moved perpendicularly along the profile of the iliac bone till its interruption at the greater sciatic foramen.

With appropriate tilting movements of the transducer, the Sciatic nerve was identified in long-axis, while it emerges from the foramen.

Once the best visualization was obtained, a block needle was inserted using an in-plane technique and a cephalocaudal direction, making sure to move the needle towards the bone edge of the greater sciatic notch, where the sciatic nerve runs. This helped to avoid the damage of the ureter or rectum and the puncture of the inferior gluteal artery, what can happen if the needle is introduced in the pelvis beyond the plexus (Figure 1).[5]

Once the nervous target was reached, the electro-neuro-stimulator was turned on, and when muscle contractions were aroused at 0.2-0.4 mA, 15 mL of 0.5% levobupivacaine were injected.

Subsequently, we proceeded with the US-guided Lumbar Plexus Block using the "Shamrock Method."[6] At this point, 15 mL of 0.5% levobupivacaine were injected.

This approach allowed us to avoid the need for gen-