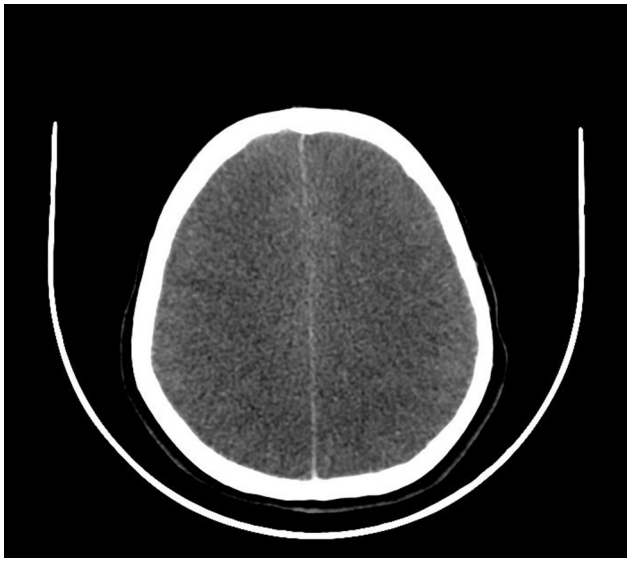

Figure 1. On the third day of admission, cranial computed tomography revealed widespread hypodense areas in both cerebral hemispheres, loss of gray and white matter separation, and deletion in sulcal structures compatible with severe edema.

(owing to possible toxicologic effects) on CT and was diagnosed with brain death on the 10th day of admission. CNS pathophysiologic effects have been hypothetically assigned to venom penetration through the blood-brain barrier because of possible increased permeability in young children.[3] Symptoms of systemic envenomation may be caused by the venom (toxins) itself or neurotransmitters (catecholamines) and proinflammatory cytokines released owing to the venom.[4]

In conclusion, we believe that this patient had unusually severe brain damage either owing to venom-related direct CNS toxicity (increased permeability of the blood-brain barrier, affecting the CNS neurons) or the secondary effect of proinflammatory cytokines and neurotransmitters affecting blood vessels, which induced brain ischemia and cytolytic brain edema.

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Methoxyflurane May Be a Suitable Analgesic for Extreme Prehospital Conditions

To the Editor:

Methoxyflurane (MEOF) is a fluorinated hydrocarbon anesthetic that was introduced to the market by Abbott Laboratories as Penthrane in the early 1960s. MEOF was found to have analgesic properties at subanesthetic doses. A disposable inhaler was developed for self-administration of MEOF for pain relief in minor surgical procedures and obstetrics in the late 1960s. In 1966, the first report of postoperative nephrotoxicity associated with MEOF emerged. Although MEOF has been withdrawn for use as an anesthetic agent, low-dose MEOF delivered via a handheld inhaler has continued to be in wide use in Australia and New Zealand since 1975. MEOF as an analgesic has been used by more than 6 million people over the course of 40 y in Australia and New Zealand. Common nonserious adverse effects are reactions such as headache, nausea, dizziness, and somnolence. Generally, adverse effects are mild and transient, resolving after inhalation is stopped. MEOF administered at analgesic doses via a disposable inhaler has recently become available in Europe for emergency treatment of moderate-to-severe pain in conscious adult trauma patients.

A recent study demonstrates that prehospital pain management is characterized by ongoing oligoanalgesia owing to undelivered analgesia.[1] Data from the control arms of the studies that compared MEOF to standard

Table 1. Summary of inhaled methoxyflurane study design in patients with trauma pain

Study	*Design*	*Primary endpoint*	*Conclusion*
Coffey et al. (2014)[4] NCT01420159 Medical Developments International	Phase 3 randomized, double blind, multicenter, placebo-controlled trial; United Kingdom; 300 patients (149 MEOF)	Change in pain intensity as measured using the VAS from baseline to 5, 10, 15, and 20 min after the start of study drug inhalation	MEOF administered with the inhaler is an efficacious, safe, and rapidly acting analgesic
Borobia et al. (2020)[2] NCT03256903 Mundipharma Pharmaceuticals	Phase 3b randomized, active-controlled, open-label, parallel-group trial performed in 13 emergency department and 1 out-of-hospital unit; Spain; 305 patients (156 MEOF)	Change from baseline in NRS pain intensity score during the first 20 min of treatment and time to first pain relief	MEOF is a nonnarcotic, easy-to-administer, rapid-acting, first-line alternative to currently available analgesic treatments for trauma pain
Mercadante et al. (2019)[8] NCT03585374 Mundipharma Pharmaceuticals	Phase 3b randomized, open-label, active-controlled, multicenter trial; Italy; 272 patients (136 MEOF)	Change in VAS pain intensity from baseline to 3, 5, and 10 min	MEOF provided superior pain relief compared with standard analgesic treatment in patients with moderate-to-severe trauma pain and may offer a simple, fast, effective, nonopioid treatment option
Lim et al. (2020)[5] NCT01887951	Prospective, phased, cluster-randomized crossover study; Singapore; 369 patients (167 MEOF)	Reduction in pain as measured by reduction in NRS at 5, 10, 15, and 20 min after treatment; time taken from arrival at scene to administration of treatment	MEOF was superior to 50 mg intramuscular tramadol in terms of analgesic efficacy, onset of effective analgesia, and speed of administration. It was also associated with better paramedic and patient satisfaction
Ricard-Hibon et al. (2020)[3] NCT03798899 Mundipharma Pharmaceuticals	Phase 3b randomized, open-label, multicenter, placebo-controlled trial; France; 351 patients (178 MEOF)	Time until pain relief ≤30 mm, as assessed on the VAS	MEOF, initiated by triage nurse as part of a multimodal analgesic approach, is effective in achieving pain relief for trauma patients. This effect was particularly pronounced in the severe pain subgroup
Marinangeli et al. (2018) (study still in progress)[6] Mundipharma Pharmaceuticals	Phase 3b prospective, single-arm, multicenter trial; Approximately 200 adult patients with a pain score of at least 4 on the NRS owing to limb trauma who were rescued by HEMS will be enrolled. Patients will receive up to 2×3 mL MEOF, self-administered by the patient by inhalation under medical supervision. Rescue medication will be permitted if required.		

HEMS, helicopter emergency medical services; MEOF, methoxyflurane; NRS, numeric rating scale; VAS, visual analog scale.

treatment revealed that trauma pain is often undertreated in current clinical practice, and there is no established standard of care. In the first randomized trial of MEOF in the emergency setting in Europe, only 23% of patients with severe pain (>7 on the numeric rating scale) received opioids in the standard-of-care arm or as a rescue medication.[2] This was also reported in a French study in which 31 patients, 18% of the control arm, did not achieve pain control.[3]

A growing body of evidence demonstrates that inhaled MEOF is well tolerated and effective in providing rapid onset of analgesia. However, few randomized controlled trials have been carried out regarding the matter. There are now several European randomized trials, summarized in Table 1. It is regrettable that 4 of these 5 trials are sponsored by the same pharmaceutical group; this should encourage great caution in interpreting the results and developing new protocols.

It would appear that MEOF is an efficacious, safe, and rapidly acting analgesic; is easy to administer as a first-line alternative to currently available analgesics; and is associated with better paramedic and patient satisfaction.[2,4,5]

The use of MEOF in hostile environments, where patient mobilization is difficult, is of particular interest because of MEOF's ease of use and speed of action. To assess whether inhaled MEOF is effective, safe, and practical in treating trauma pain in remote and hostile environments, a prospective, single-arm, multicenter trial was designed. This Italian study is currently ongoing and enrolling approximately 200 patients with single-limb trauma.[6] The first patient was enrolled in March 2019.

In prehospital settings, where interventions are performed by a variety of professionals where and physicians may not be present, administration of MEOF is practical, with a safe administration route and rapid onset of action. The inhaler is lightweight, robust, and easy to use, even with gloved hands, and it requires minimal training for effective use. It can be easily transported and stored at a wide range of temperatures (−20 to 40°C). In a case report, MEOF provided rapid, effective analgesia for visceral and procedural pain at an altitude of 4470 m.[7] Currently, treatment is to be supervised by a healthcare professional and is self-administered through patient-controlled analgesia. MEOF may be particularly relevant in patients who are able to self-administer analgesia while isolated in hostile environments.

Low-dose MEOF administered via a handheld inhaler has provided well-tolerated, short-term pain relief for trauma patients for many years. The availability of a nonnarcotic, well-tolerated, rapid-acting, and effective treatment option may improve acute trauma pain management. The ease of use of MEOF may make it particularly useful in the management of acute pain in hostile environments. MEOF could be a suitable option in the following situations:

- For emergency prehospital doctors—more specifically, when involved in mountain rescue
- For paramedics and mountain rescuers while waiting for the arrival of medicalization or transfer to the hospital
- For the victim, in the context of self-medication, particularly in isolated environments

To date, several randomized trials support the use of MEOF, and it is probably time to carry out a meta-analysis on this subject.

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Can't See the Wood for the Trees

To the Editor:

While revising for examinations recently, I found myself staring out the window at the trees and an unusual thought occurred to me. I noticed during the clinical examination of compartment syndrome, uterine rupture, and Ludwig's angina, several sources use the tactile sensation of "woody tense" to describe all of these different entities. In university, I remember learning the subtleties of breath sounds with a stethoscope, but I never recall being schooled on the sensation of wood. A literature review demonstrated no fewer than 8 different serious medical conditions associated with the same "woody tense" sensation from thyroiditis to zygomycosis and from priapism to pyomyositis.[1-6] Based on this review, I concluded that the sensation of "woody tense" has a strong association with potentially dangerous conditions. This similar clinical finding in multiple serious pathologies is an unusual phenomenon. The sensitivity and specificity of this finding is unknown and will vary from condition to condition. I believe the description of this phenomenon is unique.

As medical professionals, we are increasingly reliant on diagnostic technologies, and this has potentially allowed us to forget this simple pearl of the clinical examination, lost in the tide of time. Our ignorance of this phenomenon somewhat reflects our treatment of wood and trees in general. Since the dawn of our species, we have used trees as shelter; as tools for hunting, protection, and war; and for warmth and cooking. We have exploited trees to advance society tremendously. Now we reject them, choosing to live lavishly, consuming and wasting in densely populated urban areas. Increasing population and urbanization coupled with politico-economic policies of mass production and consumption have led to deforestation on an enormous scale. These factors are exacerbating climate change, increasing our susceptibility to transmissible disease, worsening our general health and happiness, and will eventually lead to the end of our species.

In antithesis to urban areas, simply walking in the woods or "forest bathing" has been demonstrated to have profound benefits for physical and mental health and has been practiced in Japan for centuries.[7] For the happiness and health of the human race, perhaps we all should return to the trees. Certainly, the medical students should.

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