J Anesth (2007) 21:540–541
DOI 10.1007/s00540-007-0559-1

Journal of
Anesthesia

Neurotoxicity of intrathecal local anesthetics

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Spinal anesthesia has been used clinically for more than 100 years, with the apparent establishment of safe puncture methods and local anesthetic effects on neuronal tissue [1]. However, in the 1990s, four cases of cauda equina syndrome (CES) were reported [2] after uneventful continuous spinal anesthesia with a high dose of local anesthetics, leading to doubt regarding the safety of intrathecal local anesthetics. Subsequently, transient radicular irritation (TRI), which is characterized by a sensory abnormality that seems to be induced by posterior root irritation, has also been recognized as a symptom of local neurotoxicity [3].

Clinical research has shown that the incidence of TRI is unexpectedly high, but that of CES is very low, and the incidence of both syndromes is higher in patients injected with lidocaine and lower in those receiving bupivacaine [4,5]. However, since patients with TRI do not always have objective neurogenic signs, unlike those with CES, it is not fully accepted that TRI is induced by neurogenic injury. Accordingly, some researchers agree that TRI and cauda equina syndrome are induced by a different mechanism, while others believe that cauda equina syndrome is a neurological symptom, but TRI is a muscular disorder [6,7]. Drasrar [8] suggested that TRI is a mild type of cauda equina syndrome. In 1997, a paper entitled "Transient radicular irritation: a misnomer?" was published in a letter to an editor [9]. In that paper, the author suggested that there is no evidence that this symptom is induced by root damage, although the complaints of patients give the impression these symptoms are caused by posterior nerve damage. Therefore, "radicular" is not a proper word for this symptom. Thereafter, the name TRI was changed to TNS (transient neurological symptoms). Furthermore, the prognoses of TRI and CES are different, and therefore the relevance of these two symptoms remains unclear.

The above reports led to wide-ranging clinical and experimental studies to assess whether CES and TRI originate from local neurotoxicity [5,10,11]. These studies all showed that local neurotoxicity worsens as the concentration of local anesthetics increases, and that toxicity is higher with lidocaine and lower with bupivacaine. However, the primary lesion and pathological mechanisms induced by local neurotoxicity were not established, suggesting that histological data are needed to define the origin of the clinical symptoms of CES and TRI. We therefore investigated the histological evidence of local neurotoxicity using two spinal injury models in rats.

In the first model, referred to as experiment 1 [12], the caudal side of a catheter tip was located at Th 13 in the subarachnoid space, and in the second model the catheter tip was located at S1 among the cauda equina nerves [13]. In both models, we concluded that neurotoxic injury was induced by local anesthetics, starting from the entry zone of the posterior root and extending

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Received: July 19, 2007

to the posterior column, based on axonal degeneration observed with light and electron microscopy. In the entry zone, the axon has no myelin sheath and is easily accessible to any drug in the cerebrospinal fluid. Our results suggest that the primary lesions and mechanisms in CES and TRI are identical. CES develops when posterior roots in the entry zone are damaged at S2–S4, i.e., the nerves responsible for bladder–rectal dysfunction, and TRI develops when damage to the same area of the posterior root occurs at L5 or S1 with intact S2–S4 nerves.

TRI is characterized by transient symptoms, but we consider that both syndromes are likely to be reversible if the histological damage is mild, and irreversible if the histological damage is severe.

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