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Intrathecal lidocaine neurotoxicity: Combination with bupivacaine and ropivacaine and effect of nerve growth factor

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ABSTRACT

Aims: The study aims to investigate the neurotoxicity induced by combined use of intrathecal lidocaine with bupivacaine and ropivacaine, and to examine the effect of nerve growth factor (NGF) on lidocaine-induced neurotoxicity.

Main methods: All rats received intrathecal infusion of anesthetics and NGF. To study the neurotoxicity of combined use of lidocaine with bupivacaine and ropivacaine, rats received saline, 5% lidocaine, 1.065% bupivacaine, 1.5% ropivacaine, 5% lidocaine + bupivacaine, or 5% lidocaine + 1.5% ropivacaine. To study the neurotoxicity of different proportions of lidocaine and bupivacaine, mixtures were made by mixing 10% lidocaine and 2.5% bupivacaine in ratios of 1:3, 1:2, 1:1, 2:1 and 3:1 by volume. To study the effect of NGF on lidocaine-induced neurotoxicity, rats received saline or 10 μg NGF for 1, 2, 5 and 8 days.

Key findings: The neurotoxicity of lidocaine was significantly increased when combined with ropivacaine. A mixture of lidocaine and bupivacaine in a ratio of ≤1:1 did not significantly increase lidocaine-induced neurotoxicity. NGF significantly reduced lidocaine-induced neurobehavioral and morphological damage in the spinal cord. This was accompanied by downregulation of caspase 3 expression.

Significance: Ropivacaine is not safe when intrathecally administered with lidocaine at the concentrations used in this study. Bupivacaine may be safely used with lidocaine at a ratio of 1:1. NGF can reduce lidocaine-induced neurotoxicity, possibly via inhibition of caspase 3-mediated apoptosis.

Introduction

Short-acting local anesthetics such as lidocaine have been widely used in the clinic for spinal anesthesia (Liu and McDonald, 2001). Neurological complications such as transient neural symptoms and cauda equina syndrome after spinal anesthesia have been reported. Increasing evidence has showed that the neurotoxicity of lidocaine is greater than that of other commonly used local anesthetics (Zaric and Pace, 2009; Johnson, 2000; Hampl et al., 1998). Other long-acting local anesthetics such as bupivacaine and ropivacaine have also been reported to induce neurotoxicity, although to a lesser extent than lidocaine (Takenami et al., 2005; Sakura et al., 2005; Radwan et al., 2002a, 2002b; Yamashita et al., 2003). For example, Sakura et al. (2005) reported that bupivacaine was less neurotoxic than lidocaine when administered intrathecally at equipotent concentrations in rats. Furthermore, Takenami et al. (2012) found that intrathecally administered ropivacaine was less neurotoxic than bupivacaine in a rat spinal model.

Clinically, combinations of short-acting anesthetics with long-acting anesthetics are used to hasten, improve or prolong neural blockade (Eckert and Standl, 1997; Nishiyama, 2012). Lidocaine in combination with bupivacaine has long been used for spinal anesthesia, and addition of lidocaine to bupivacaine reduces the duration of the spinal block and is associated with a shorter recovery time (Yazicioglu et al., 2013; Lee et al., 2008). Combination of ropivacaine and lidocaine has been used in interscalene block and spinal anesthesia (Nishiyama, 2012; Kallio et al., 2006). However, it remains unclear whether combined use of lidocaine with long-acting bupivacaine or ropivacaine increases neurotoxicity in comparison with lidocaine alone.

The mechanisms underlying lidocaine-induced neurotoxicity have not yet been elucidated. It has been reported that lidocaine-induced neurotoxicity involves mitochondrial injury and caspase activation (Johnson et al., 2004), mitochondria-dependent apoptosis (Werdehausen et al., 2007) and activation of p38 mitogen-activated protein kinase (Lirk et al., 2007). In addition, intrathecal injection of lidocaine causes increased release of cerebrospinal fluid glutamate (Cherng et al., 2011), which produces excitotoxic effects and induces neuronal cell death. Lidocaine-induced increase in the intracellular Ca^{2+} concentration has also been attributed to its neurotoxicity (Kanai et al., 2001; Johnson et al., 2002).

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Table 1
The experimental procedure of the effect of NGF on lidocaine-induced neurotoxicity.

	0 day	1 days	2 days	3 days	4 days	5 days	6 days	7 days	8 days
P0	–								
P1	*								
P2	*	+							
P5	*	+	+	+	+				
P8	●*	●+	●+	●+	●+	●+	●+	●+	●

–, sham operation with catheter insertion only; *, intrathecal injection of 20% lidocaine; +, intrathecal injection of NGF\NS; ●,behavioral test.

Identification of factors that reverse lidocaine-induced neurotoxicity is important for clinical application of lidocaine in spinal anesthesia.

Nerve growth factor (NGF), a protein belonging to a family of neurotrophic factors called neurotrophins, can promote survival, growth and regeneration of neurons (Manni et al., 2013). Cao et al. (2002) reported that NGF protected injured nerve tissues via inhibiting neuronal apoptosis in a rat model of spinal cord injury. In addition, it has been reported that NGF can protect neurons by inhibiting glutamate-mediated excitotoxicity and reducing intracellular Ca^{2+} concentration (Llado et al., 2004; Jiang et al., 2008). Therefore, NGF is a potential neurotrophic factor that may prevent lidocaine-induced neurotoxicity.

In the present study, we investigated the neurotoxic effect of intrathecal injection of lidocaine or its combination with bupivacaine and ropivacaine in rats. The purpose of this study was to investigate the neurotoxicity of the combined use of lidocaine with bupivacaine and ropivacaine, to evaluate the neurotoxic effect of different proportions of lidocaine and bupivacaine, and to examine the effect of NGF on lidocaine-induced neurotoxicity.

Materials and methods

Animals

All experimental protocols were approved by the Institutional Animal Care and Use Committee of China Medical University. Adult Sprague Dawley rats (male, weighing 281 ± 17 g) were used in this study. The animals were obtained from the Animal Care Center of China Medical University. Animals were housed at room temperature (25 ± 5 °C) with a 12 h light/dark cycle. Animals were fed standard rat chow and water ad libitum.

Intrathecal injection

An intrathecal catheter was inserted as previously described by Sakura et al. (2005). Briefly, rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (300–350 mg/kg). A heat-connected polyethylene catheter (PE-10) was inserted into the subarachnoid space through the L4–L5 intervertebral space and advanced by 2 cm in the caudal direction. The insertion of the catheter into the subarachnoid space was verified by cautious aspiration of cerebrospinal fluid (CSF). Rats showing obvious hindlimb paralysis were excluded from the study. The catheter was then flushed with normal saline (10 μl) to prevent thrombus formation. The distal end of the catheter was closed by heating to prevent CSF leakage. The catheter was then fixed subcutaneously. Rats were then housed individually for 3 days. Three days after catheter insertion, lidocaine (1%, 20 μl) was injected through the catheter. Rats showing obvious hindlimb paralysis (lidocaine-positive) were included in the study.

To study the neurotoxicity of combined use of lidocaine with bupivacaine and ropivacaine, forty-eight lidocaine-positive rats were randomly assigned to 6 groups: control group (Group S, 0.9% saline, n = 8), 1.065% bupivacaine group (Group B, n = 8), 1.5% ropivacaine group (Group R, n = 8), 5% lidocaine group (Group L, n = 8), 5% lidocaine + 1.065% bupivacaine group (Group LB, n = 8), and 5% lidocaine + 1.5% ropivacaine group (Group LR, n = 8). It is to be noted that 1.065% bupivacaine, 1.5% ropivacaine and 5% lidocaine are equipotent anesthetic concentrations. Each rat received the same volume of anesthetics (20 μl). For the LB and LR groups, lidocaine (10 μl) was mixed with equal volume of bupivacaine and ropivacaine, respectively.

In the clinic, lidocaine is commonly mixed with bupivacaine in ratios of 1:3, 1:2, 1:1, 2:1, or 3:1 by volume (Camorcia et al., 2008; Cuvillon et al., 2009).

To study the neurotoxicity of different proportions of lidocaine and bupivacaine, forty-eight lidocaine-positive rats were randomly assigned to 6 groups: control group (Group S, 0.9% saline, n = 8), 2.5% lidocaine + 1.875% bupivacaine group (Group LB13, a mixture of 10% lidocaine and 2.5% bupivacaine in a ratio of 1:3 by volume, n = 8), 3.33% lidocaine + 1.67% bupivacaine group (Group LB12, a mixture of 10% lidocaine and 2.5% bupivacaine in a ratio of 1:2 by volume, n = 8), 5% lidocaine + 1.25% bupivacaine group (Group LB11, a mixture of 10% lidocaine and 2.5% bupivacaine in a ratio of 1:1 by volume, n = 8), 6.67% lidocaine + 0.83% bupivacaine group (Group LB21, a mixture of 10% lidocaine and 2.5% bupivacaine in a ratio of 2:1 by volume, n = 8), and 7.5% lidocaine + 0.625% bupivacaine group (Group LB31, a

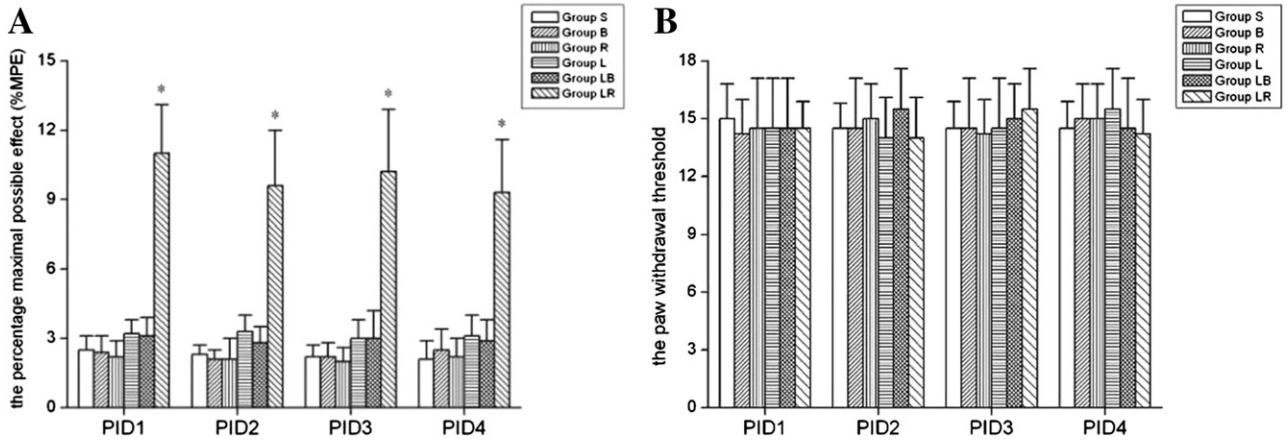

Fig. 1. The effects of lidocaine and its combination with bupivacaine and ropivacaine on tail-flick latency and paw withdrawal threshold. A.B. The percentage maximal possible effect (%MPE) in the tail-flick test (A), and the paw withdrawal threshold in the paw withdrawal test (B) at 1, 2, 3 and 4 days after intrathecal administration of 0.9% saline (Group S), 1.065% bupivacaine (Group B), 1.5% ropivacaine (Group R), 5% lidocaine (Group L), 5% lidocaine + 1.065% bupivacaine (Group LB), and 5% lidocaine + 1.5% ropivacaine (Group LR). A. %MPE was calculated as follows: $(T_1 - T_0) / (T_2 - T_0) \times 100$, where T_0 and T_1 were the tail-flick latencies obtained before and after drug application, and T2 was the cut-off time. *$P < 0.05$ vs Groups S, B, R, L, and LR, n = 8. B. The paw withdrawal threshold. No significant differences were found among groups, n = 8.