Title: Prolonged postoperative analgesia using a slow release long acting local anesthetic formulation

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Abstract

Background: Current management of postoperative pain includes multiple injections of short acting local anesthetic solutions which demands expensive equipment and close monitoring.

Research Hypothesis: Local administration of high doses of local anesthetic agents could prolong the local anesthetic effects for a few days or even weeks via a slow controlled release injectable implant.

Aims: The aim was to evaluate the efficacy of high doses of local anesthetic agent loaded into an improved slow-release fatty acid based biodegradable polymer in prolonging motor and sensory block when injected locally.

Methods: Bioadhesive liquid compositions of a polymer based on castor oil (PLA-CO) were prepared together with local anesthetic agent bupivacaine. Degradation and release of the local anesthetic agent and polymer were measured in vitro. The formulation was applied to the sciatic nerve and the efficacy of the anesthesia provided (sensory and motor) nerve blockade were measured. Toxicity (blood/tissues) and pathological effects of the drug-polymer formulation were investigated.

Results: The polyesters were synthesized from DL-Lactic acid and castor oil with feed ratio of 4:6 and 3:7 w/w. The DL-Lactic acid co castor oil p(DLLA:CO) 3:7 released 65% of the incorporated bupivacaine during 1 week in vitro. Bupivacaine was incorporated in the polymer without affecting the polymer molecular weight. P(DLLA:CO) 3:7 was used for in vivo experiments due to easier injection. Peak bupivacaine plasma concentration, t\text{max}, was 3 hours post injection. Single injection of 10% bupivacaine loaded into p(DLLA:CO) 3:7 caused motor block duration of 24h and sensory block duration 48h. The mice receiving p(DLLA-CO) 3:7 -15% bupivacaine had sensory block duration of 96h. Viscosity of 10% and 15% bupivacaine-p(DLLA:CO)3:7 formulations was reduced using the hydrophobic additives castor oil and ricinoleic acid, while retaining prolonged sensory block duration, of 72h. Regarding neuro-myotoxicity, complete resolution seen 3 months following injection.

Discussion: Several formulations have been described for providing prolonged local anesthetic action. However many caused systemic toxicity, neurotoxicity or myotoxicity were poorly injectable or expensive to prepare. One of the obstacles to overcome is the progress from animal to clinical studies. Although the dose required for human nerve analgesia was predicted to be 200 fold higher than that required for rat analgesia in practice it may be only 5-10 fold higher. The proposed polymer-bupivacaine formulation is easily prepared and provides analgesia for at least 96 hours. It does not cause systemic toxicity at therapeutic doses. Neurotoxicity and myotoxicity are present initially as expected, however these effects are reversible.

Conclusions: Site directed application of a slow release encapsulated local anesthetic formulation is effective for a prolonged time period of days against postoperative pain in vivo, with minimal toxicity.

Key words Analgesia; Bupivacaine; Encapsulation; Polymer; Prolonged
Publications and patents associated with the project (in PubMed format)


