Risks of Precipitate Formation When Combining Corticosteroids with Local Anesthetic for Use During Interventional Pain Procedures

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Myth: Corticosteroids can be mixed with local anesthetics for injection during interventional spine procedures without concern for adverse consequences due to the interactions between two agents combined for injection.

Fact: There is *in vitro* evidence that ropivacaine precipitates crystal formation larger than the diameter of an arteriole when combined with either dexamethasone or betamethasone.

Rationale for Use of Local Anesthetics in Epidural Steroid Injections

Interventional procedures for pain, such as transforaminal epidural steroid injections (TFESI), involve instilling corticosteroid preparations at specific sites from which pain originates. Local anesthetics often have a role in such injections, mitigating the index pain and providing evidence of the site and distribution of the injectate.

Pharmacology

Various local anesthetic agents precipitate (crystallize) at specific pH levels. In order of pH, ropivacaine crystallizes at pH 6.9, which is close to a neutral pH of 7.0 and more acidic than a physiologic pH, which ranges from 7.35-7.45 in normal human arterial blood [1]. Bupivacaine crystallizes at pH 7.7 and lidocaine crystallizes at pH 12.9. As pH increases, the likelihood of precipitation (crystallization) increases [2]. Adding certain corticosteroid preparations to local anesthetics increases the pH of the resultant mixture and may cause crystallization.

Relevant Studies

Two *in vitro* studies have investigated the possibility of corticosteroids causing the precipitation of local anesthetics. In 2015 Watkins *et al.* reported macroscopic and microscopic observations of ropivacaine crystal formation when mixed with dexamethasone [3]. The degree of crystallization had a positive correlation with higher pH and with higher concentrations of dexamethasone (10mg/mL vs. 4mg/mL). Crystallization did not occur when lidocaine or bupivacaine were mixed with dexamethasone, even when these solutions were alkalinized with the agent sodium bicarbonate (commonly mixed with local anesthetics clinically to reduce pain during injection) [4].

In 2016 Hwang *et al.* reported observations of three corticosteroid preparations triamcinolone, betamethasone, and dexamethasone, when each was mixed with lidocaine, bupivacaine, and ropivacaine [2]. Betamethasone caused crystal precipitation of both ropivacaine and bupivacaine at physiologic pH levels (pH 7.5 and 7.7, respectively). Ropivacaine precipitates were substantially larger than the diameter of an arteriole at >300 micrometers in length [5]; bupivacaine precipitates were smaller than the diameter of a red blood cell (RBC) at only a few micrometers in length [6]. Dexamethasone caused crystal precipitation of ropivacaine at physiologic pH levels (pH 7.0); these crystals were also substantially larger than the diameter of an arteriole at >300 micrometers in length [5]. This phenomenon was not observed when mixing lidocaine with triamcinolone, betamethasone, or dexamethasone. Triamcinolone did not precipitate crystal formation of any of the three local anesthetics investigated. In summary, this study demonstrated that ropivacaine is capable of forming crystals larger than an arteriole at physiologic pH levels in the presence of both the dexamethasone (a non-particulate agent in its independent state) and betamethasone. While these results were observed at room temperature, the authors note that warming the crystalized solutions to 40°C did not dissolve the precipitates.

	Methylprednisolone	Triamcinolone	Betamethasone	Dexamethasone
Lidocaine	Unknown crystallization Particulates present	No crystallization Particulates present	No crystallization Particulates present	No crystallization No particulates
Bupivacaine	Unknown crystallization Particulates present	No crystallization Particulates present	Crystallization small^ Particulates present	No crystallization No particulates
Ropivacaine	Unknown crystallization Particulates present	No crystallization Particulates present	Crystallization large* Particulates present	Crystallization large* No particulate

^Crystals were smaller than the diameter of a RBC at only a few micrometers in length [6].
*Crystals were substantially larger than the diameter of an arteriole at >300 micrometers in length [5].

Clinical Implications

When planning a targeted interventional pain procedure involving the injection of corticosteroid combined with a local anesthetic, consideration should be given to the possible formation of large crystal precipitates. Any crystal larger than the diameter of an RBC (6 – 8 microns) could potentially obstruct arterioles with ensuing occlusion and tissue ischemia. This is of particular concern when considering the implications of inadvertent arterial injection during TFESI or any other procedure performed in close proximity to the arterial supply of neural structures.

Recommendations

- Because of anatomic variability with regards to radicular arteries within the neuroforamen, safe TFESI must take into account both technical needle placement and characteristics of injected agents.
- Particulate steroids and mixtures of steroid and local anesthetics that produce crystals should be strictly avoided in cervical TFESI.
- Dexamethasone is a non-particulate steroid and remains the preferred corticosteroid for TFESI.
- Dexamethasone may safely be combined with either lidocaine or bupivacaine but because of crystallization should not be combined with Ropivacaine.
- For TFESI, the safest protocol is that described in the SIS *Practice Guidelines* [7].

References

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