

Non-Particulate Steroids (Betamethasone Sodium Phosphate, Dexamethasone Sodium Phosphate, and Dexamethasone Palmitate) Combined with Local Anesthetics (Ropivacaine, Levobupivacaine, Bupivacaine, and Lidocaine): A Potentially Unsafe Mixture

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Purpose: Particulate steroids used in epidural steroid injections have been suspected as a cause of post-procedural embolic events. Some particulate steroids have been suspended only when the transforaminal approach is used for an epidural block of the spine. In contrast, non-particulate steroids are generally accepted for safety during epidural steroid injections. However, the safety of using a mixture of non-particulate steroids and local anesthetics is unknown. This study analyzed whether mixtures of commonly used non-particulate steroids and local anesthetics form crystals in solution.

Methods: We mixed non-particulate steroids (betamethasone sodium phosphate, dexamethasone sodium phosphate, and dexamethasone palmitate) and local anesthetics (ropivacaine, levobupivacaine, bupivacaine, and lidocaine) at different ratios. We used fluorescence microscopy to observe whether crystals formed in mixed solutions; we also measured the pH of each steroid, local anesthetic, and the mixtures.

Results: Ropivacaine or levobupivacaine and betamethasone sodium phosphate produced large crystals (>50 μm). Ropivacaine or levobupivacaine and dexamethasone sodium phosphate produced small crystals (<10 μm). Lidocaine and all non-particulate steroids produced no identifiable crystals; dexamethasone palmitate and all local anesthetics did not form significant particulates. Betamethasone sodium phosphate and dexamethasone sodium phosphate demonstrated basic pH, while all local anesthetics demonstrated acidic pH. Mixtures showed a wide pH range.

Conclusion: Non-particulate steroids can form crystals upon combination with local anesthetics. Crystal formation may be caused by alkalization of steroids. The mixing of ropivacaine or levobupivacaine and betamethasone sodium phosphate may require caution during an epidural steroid injection. Lidocaine or bupivacaine is recommended as a local anesthetic. Dexamethasone palmitate is a candidate for a mixture, but additional studies on its safety and effectiveness are needed.

Keywords: epidural space, injections, lidocaine, local anesthetics, particle size, steroids

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Introduction

Epidural steroid injection (ESI) is used for the treatment of spinal pain, and the number of treated cases has increased sharply.¹ However, questions remain

regarding the effects and safety of different ESI approaches (eg, an interlaminar or transforaminal approach) or the use of specific drugs (eg, non-particulate steroids or particulate steroids).^{2–6} In particular, the cause of catastrophic complications after ESI, such as cerebral or spinal cord infarct, as well as transient ischemic attack,^{7–9} may be related to the injection of particulate steroids. Particulate steroids may work as an embolus if injected into spinal branches that have anastomosed with the vertebral artery; when cervical transforaminal ESI (TFESI) was performed, these embolic events were reported frequently.^{7,9–11}

These events attracted the attention of the US Food and Drug Administration (FDA); in April 2014, the FDA issued a warning of serious neurologic complications after ESI and implemented label changes.^{12,13} The Anesthetic and Analgesic Advisory Committee was formed in November of the same year. This committee recommended a contraindication for transforaminal cervical injections with particulate steroids because of the concern of catastrophic complications. In addition, a multidisciplinary working group, which held discussions to establish the safe use of ESI, together with thirteen specialty stakeholder societies, issued 17 suggestions for the safe use of ESI.¹⁴ Among these 17 suggestions, five involve the use of particulate steroids (eg, methylprednisolone, triamcinolone acetate, and betamethasone acetate) in ESI. These suggestions recommended the use of non-particulate steroids because TFESI with particulate steroids, regardless of spine level, could cause embolic events. Ultimately, the key aspect of this warning was that the use of material that can cause embolic events during TFESI must be reconsidered.

Mixtures of local anesthetics and non-particulate steroids have been used in common practice. However, the ESI regimen is highly varied, and there are no guidelines. However, the safety of this mixture (ie, whether it makes particulates or not) has not been considered carefully. The first aim of this study was to analyze mixtures of commonly used non-particulate steroids (betamethasone sodium phosphate, dexamethasone sodium phosphate, and dexamethasone palmitate) and local anesthetics to determine the safest combination of steroid and local anesthetic for use. The second aim was to suggest a safe regimen for TFESI (eg, through the use of dexamethasone palmitate).

Materials and Methods

We mixed three non-particulate steroids and four local anesthetics in different ratios. We examined whether

these mixtures produced crystals in each mixed solution. In addition, the pH of each mixture was measured.

Non-Particulate Steroids and Local Anesthetics

Three non-particulate steroids were used in this study: (1) betamethasone sodium phosphate 5.2 mg/mL (BSP, Betamethasone Sodium Phosphate Injection[®], Daewon Pharm, Seoul, Korea); (2) dexamethasone sodium phosphate 5 mg/mL (DSP, Dexamethasone sodium Phosphate Injection[®], Yuhan, Seoul, Korea) as a water-soluble steroid; and (3) dexamethasone palmitate 4 mg/mL (DPA, Limethason Injection[®], Mitsubishi Tanabe Pharma Korea, Seoul, Korea) as a fat-soluble steroid. Three local anesthetics were utilized: (1) ropivacaine HCl 0.75% (Ropivacaine, Ropiva[®], Hanlim Pharm, Seoul, Korea); (2) levobupivacaine HCl 0.75% (levobupivacaine, Chirocaine Injection[®], Abbott Korea, Seoul, Korea); (3) hyperbaric bupivacaine HCl 0.5% (Bupivacaine, Marcaine heavy injection[®], AstraZeneca AB, Seoul, Korea), and (4) lidocaine HCl 1% (lidocaine, LidocaineHCl Injection[®], Daihan Pharm, Seoul, Korea). Additionally, we mixed each non-particulate steroid with normal saline for comparison with the mixtures of non-particulate steroids and local anesthetics.

Microscopic Analysis of Mixtures

Each non-particulate steroid (0.5 mL) was mixed with normal saline and each local anesthetic (0.5, 1.0, and 1.5 mL) at 1:1, 1:2, and 1:3 ratios on a prepared glass slide. After placement under a cover slip, each slide was examined using a fluorescence microscope (Axioskop 2[®]; Carl Zeiss Incorporated, Jena, Germany) in four areas (two areas with the most crystals and two areas with the least crystals) at two magnifications ($\times 100$ and $\times 200$) within 1 min; a total of eight photos were taken for each slide. Images were analyzed using the Axiovision Rel. 4.8[®] (Carl Zeiss Inc., Jena, Germany). If crystals were observed in the mixed solution, we grouped the crystals into the following size groups: 0–10, 11–20, 21–50, 51–100, >100, and >500 μm . The number of crystals per size was determined by calculating the average of four areas (two high-density and two low-density) at $\times 100$ magnification. Additionally, if the mixed solutions contained crystals, they were heated at 36–37 $^{\circ}\text{C}$ for 10 min. Then, we reanalyzed the solutions by fluorescence microscopy to determine whether the crystals could melt.

Measurement of pH

First, the pH of each steroid and local anesthetic was measured. Second, each non-particulate steroid (0.5 mL) was mixed with normal saline and each local anesthetic (0.5, 1.0, and 1.5 mL) at 1:1, 1:2, and 1:3 ratios. The pH of each mixture was measured using a glass electrode pH meter (Inolab level 1, WTW Weilheim, Germany) with a biotrode electrode (Hamilton, Bonaduz, Switzerland) at room temperature.

Statistical Analysis

Statistical analyses were performed using the SPSS Statistics software (version 21.0; IBM Corp, Armonk, NY, USA). Chi-square analyses were used to compare the proportion of particles 0–10, 11–20–21–50,–, 51–100, and greater than 100, 500 among mixtures according to each ratio in local anesthetics and non-particulated steroids. In all analyses, a two-sided *P*-value < 0.05, was considered statistically significant.

Results

Microscopic Analysis of Mixtures

All steroids, including BSP, DSP, and DPA, were pure liquids with no identifiable particles (Figure 1). Table 1 shows the number of crystals per size (0–10, 11–20, 21–50, 51–100, >100, and >500 μm) for each mixture of normal saline, local anesthetics, and non-particulate steroids. Each figure shows a microscopic analysis of the mixtures.

Betamethasone Sodium Phosphate (BSP)

No crystals were observed in the mixture of BSP and normal saline. BSP and ropivacaine produced long rod-like and lucent crystals (Figure 2A). The crystals formed high-density aggregates; the common size of the crystals was 20 μm to >50 μm (Figure 2B, Table 1). BSP and ropivacaine produced crystals >50 μm in size more frequently than BSP and other local anesthetics (Table 1). Only the mixture of BSP and ropivacaine produced crystals > 500- μm in size. There were no significant differences in the number of

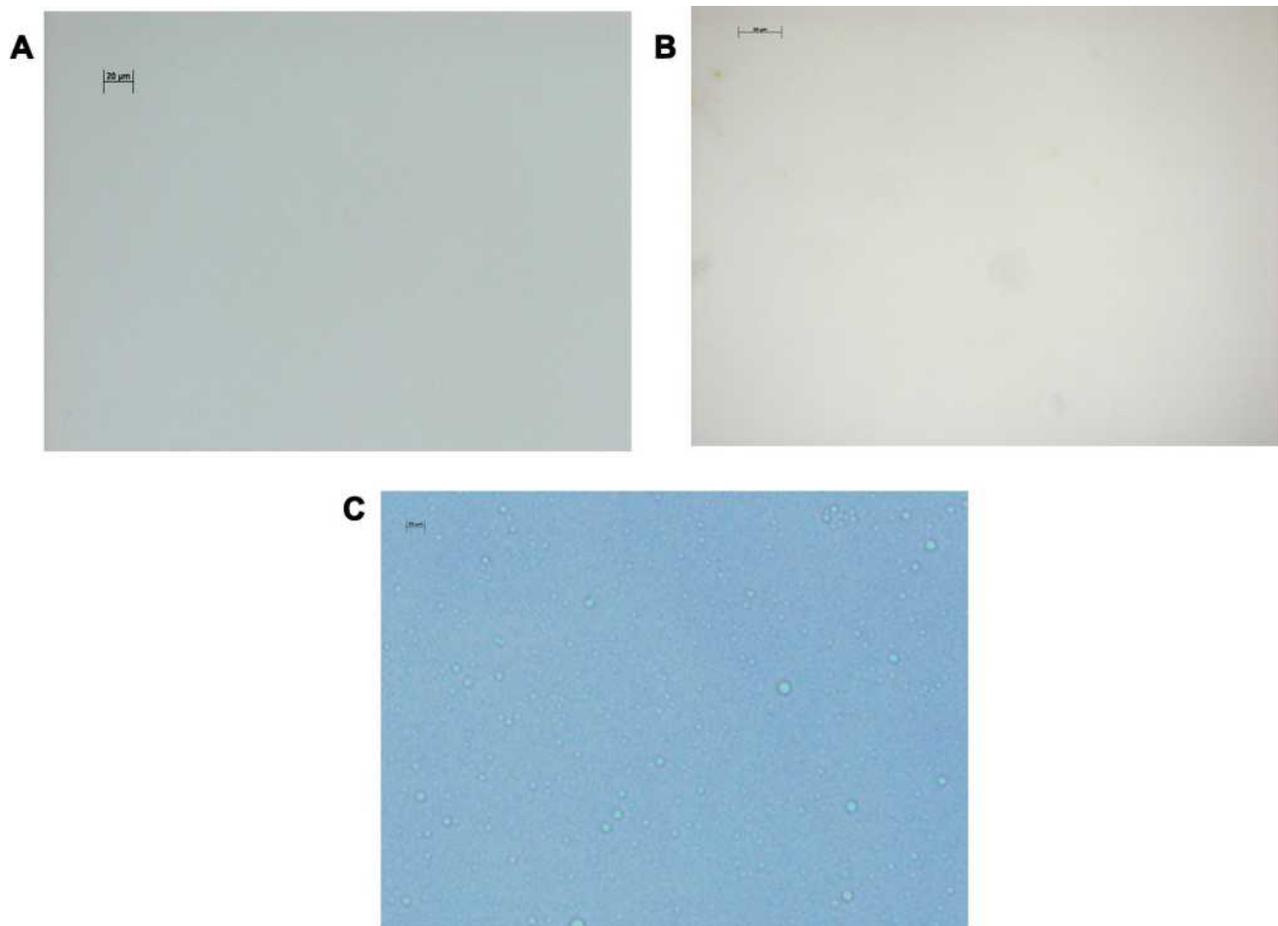


Figure 1 Non-particulate steroids were pure liquid with no identifiable particle. (A) Microscopic findings of betamethasone sodium phosphate (BSP) ($\times 200$), (B) dexamethasone sodium phosphate (DSP) ($\times 200$), (C) dexamethasone palmitate (DPA) ($\times 200$).

Table I Particulate Size Distribution in Mixed Solutions (Normal Saline or Local Anesthetics and Non-Particulate Steroids)

Non-Particulate Steroids	Normal Saline or Local Anesthetics	Dilution	No. of Particulates (%)	Particulate Distribution				>100 μm	>500 μm	P-value
				0–10 μm	11–20 μm	21–50 μm	51–100 μm			
Betamethasone sodium phosphate 5.2 mg/mL	0.9% Normal saline	1:1	0	0	0	0	0			
		1:2	0	0	0	0				
		1:3	0	0	0	0				
	0.75% ropivacaine HCl	1:1	183	15(8.2)	29(15.3)	47(25.4)	66(36.6)	14(7.8)	12(6.7)	0.84
		1:2	176	11(6.3)	26(14.8)	50(28.4)	64(36.4)	12(6.8)	13(7.3)	
		1:3	169	12(7.1)	25(14.9)	49(29.9)	52(30.8)	19(11.2)	10(6.1)	
	0.75% levobupivacaine HCl	1:1	104	8(7.7)	13(12.5)	38(36.5)	27(26)	18(17.3)	0(0)	0.99
		1:2	100	7(7)	14(14)	36(36)	28(28)	15(15)	0(0)	
		1:3	94	5(5.3)	15(16)	35(37.2)	22(23.4)	17(18.1)	0(0)	
	0.5% bupivacaine HCL	1:1	93	83(89.2)	10(10.8)	0	0	0	0	0.05
		1:2	81	78(96.3)	3(3.7)	0	0	0	0	
		1:3	75	73(97.3)	2(2.7)	0	0	0	0	
	1% lidocaine HCl	1:1	3	1	2	0	0	0	0	0.7
		1:2	2	1	1	0	0	0	0	
		1:3	0	0	0	0	0	0	0	
Dexamethasone disodium phosphate 4 mg/mL	0.9% Normal saline	1:1	0	0	0	0	0	0	0	
		1:2	0	0	0	0	0	0	0	
		1:3	0	0	0	0	0	0	0	
	0.75% ropivacaine HCl	1:1	756	452(59.8)	296(39.2)	8(1)	0	0	0	0.36
		1:2	708	421(59.5)	281(39.7)	6(0.8)	0	0	0	
		1:3	641	387(60.4)	253(39.5)	1(0.1)	0	0	0	
	0.75% levobupivacaine HCl	1:1	565	398(70.4)	142(25.1)	25(4.5)	0	0	0	0.56
		1:2	501	362(72.3)	121(24.2)	18(3.5)	0	0	0	
		1:3	472	345(73.1)	115(24.4)	12(2.5)	0	0	0	
	0.5% bupivacaine HCL	1:1	51	48(94.1)	3(5.9)	0	0	0	0	0.65
		1:2	43	42(97.7)	1(2.3)	0	0	0	0	
		1:3	31	30(96.8)	1(3.2)	0	0	0	0	
	1% lidocaine HCl	1:1	7	6	1	0	0	0	0	0.58
		1:2	5	5	0	0	0	0	0	
		1:3	2	2	0	0	0	0	0	
Dexamethasone palmitate 5 mg/mL	0.9% Normal saline	1:1	0	0	0	0	0	0	0	
		1:2	0	0	0	0	0	0	0	
		1:3	0	0	0	0	0	0	0	
	0.75% ropivacaine HCl	1:1	0	0	0	0	0	0	0	
		1:2	0	0	0	0	0	0	0	
		1:3	0	0	0	0	0	0	0	
	0.75% levobupivacaine HCl	1:1	0	0	0	0	0	0	0	
		1:2	0	0	0	0	0	0	0	
		1:3	0	0	0	0	0	0	0	
	0.5% bupivacaine HCL	1:1	0	0	0	0	0	0	0	
		1:2	0	0	0	0	0	0	0	
		1:3	0	0	0	0	0	0	0	

(Continued)

Table 1 (Continued).

Non-Particulate Steroids	Normal Saline or Local Anesthetics	Dilution	No. of Particulates (%)	Particulate Distribution				>100 μm	>500 μm	P-value
				0–10 μm	11–20 μm	21–50 μm	51–100 μm			
	1% lidocaine HCl	1:1	0	0	0	0	0	0	0	
		1:2	0	0	0	0	0	0	0	
		1:3	0	0	0	0	0	0	0	

crystals when the dilution ratios (1:1, 1:2, and 1:3) of ropivacaine with BSP ($P = 0.84$) were increased (Table 1). This result was observed not only for BSP, but also for other steroids. BSP and levobupivacaine produced not only >50- μm crystals, but also >100- μm crystals (Figure 2C and D), similar in shape to those in the mixture of BSP and ropivacaine. The distribution of the crystal sizes was similar. However, this mixture did not produce crystals >500- μm in size. In addition, there was no significant difference in the dilution ratios of levobupivacaine ($P = 0.99$). BSP and bupivacaine typically formed dot-shaped crystals <10 μm in size (Figure 2E). These crystals formed lower-density aggregates than ropivacaine or levobupivacaine with BSP. Additionally, there were no differences in the number of crystals based on changes in the ratios. BSP and lidocaine did not produce identifiable crystals, except in one or two cases (< 20 μm) (Figure 2F).

Dexamethasone Sodium Phosphate (DSP)

There were no crystals in the mixture of normal saline and DSP. DSP and ropivacaine formed short rod-shaped crystals ($\leq 10 \mu\text{m}$) (Figure 3A and B). Mixtures of DSP and ropivacaine formed small aggregates but exhibited the largest number of crystals among all mixtures. Moreover, DSP and levobupivacaine produced dot-shaped or short rod-like particulates ($\leq 10 \mu\text{m}$) (Figure 3C and D). These crystals formed aggregates with a slightly lower density than ropivacaine with DSP. The mixture of DSP and bupivacaine generated dot-shaped crystals <10 μm in number (Figure 3E). Furthermore, DSP and lidocaine did not produce any identifiable crystals (Figure 3F). Overall, mixtures of DSP and local anesthetics produced smaller, more numerous crystals than mixtures of BSP and local anesthetics. There were no differences in the number of crystals based on the changes in the dilution ratios in all mixtures.

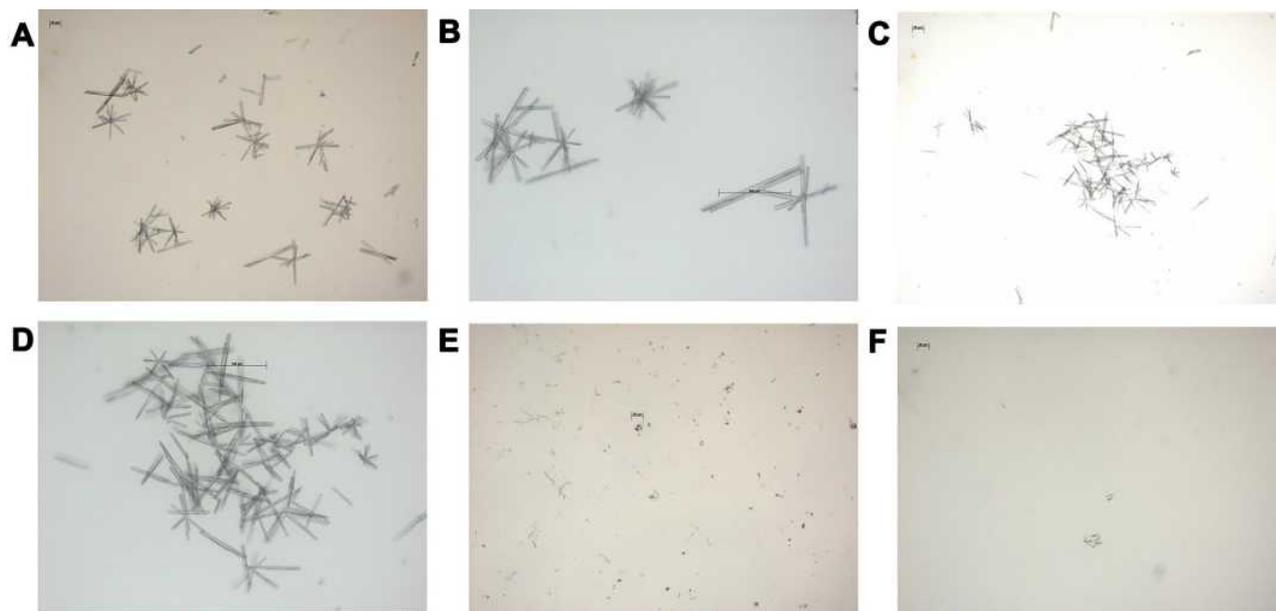


Figure 2 (A) Microscopic findings of betamethasone sodium phosphate (BSP) mixed with 0.75% ropivacaine HCl (ropivacaine) ($\times 100$). (B) High density and extremely large particulates ($>500 \mu\text{m}$) in BSP mixed with ropivacaine ($\times 200$). (C) BSP mixed with 0.75% levobupivacaine HCl (levobupivacaine) ($\times 100$). (D) High density and large particulates ($>100 \mu\text{m}$) in BSP mixed with levobupivacaine ($\times 200$). (E) BSP mixed with hyperbaric bupivacaine HCl ($\times 100$). This shows dot-shaped particulates (<10 μm). (F) BSP mixed with 1% lidocaine HCl ($\times 100$). No identifiable particulate is observed.

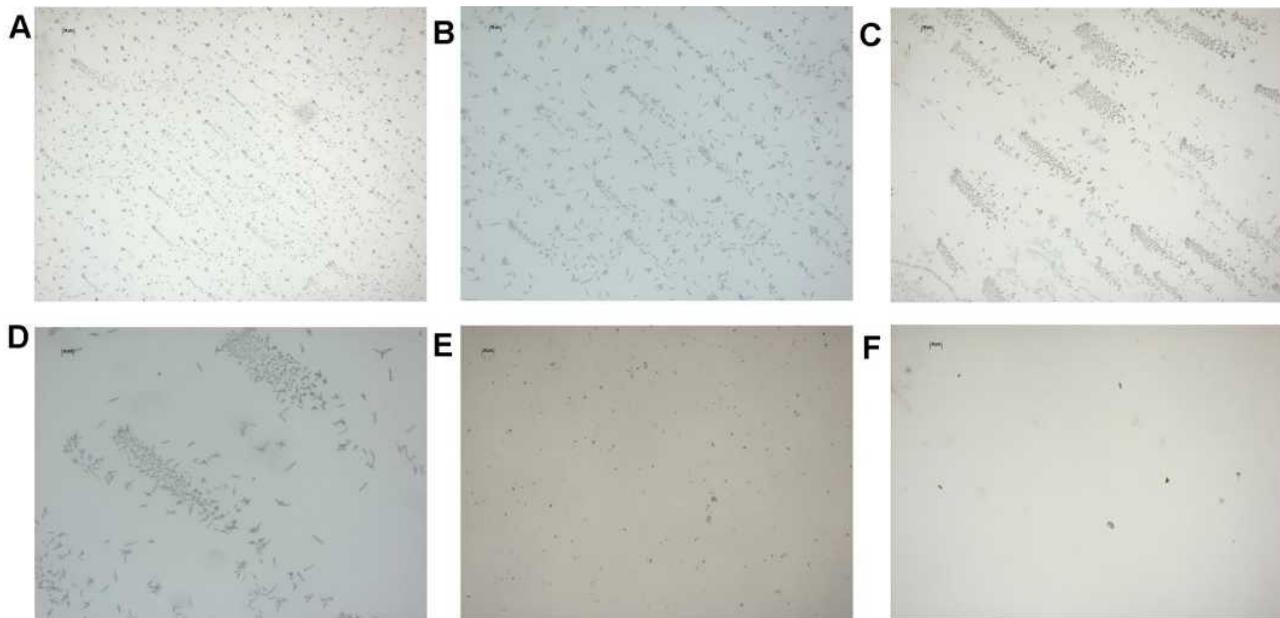


Figure 3 (A) Microscopic findings of dexamethasone sodium phosphate (DSP) mixed with 0.75% ropivacaine HCl (ropivacaine) ($\times 100$). (B) Small and short rod-like shaped particulates ($\leq 10 \mu\text{m}$) in DSP mixed with ropivacaine ($\times 200$). (C) DSP mixed with 0.75% levobupivacaine HCl (levobupivacaine) ($\times 100$). (D) Small and short particulates in DSP mixed with levobupivacaine ($\times 200$). (E) DSP mixed with hyperbaric bupivacaine HCl ($\times 100$). (F) DSP mixed with 1% lidocaine HCl ($\times 100$). No identifiable particulate is observed.

Dexamethasone Palmitate (DPA)

No crystals were observed in the mixtures of DPA and normal saline. DPA and all local anesthetics did not form significant crystals; only lipid microspheres were observed (Figure 4).

Heating of Particulates

When ropivacaine and levobupivacaine were mixed with BSP or DSP, crystals of various shapes and sizes were

produced. After we attempted to melt the produced crystals at $36\text{--}37^\circ\text{C}$, we analyzed the remaining crystals using fluorescence microscopy. However, all crystals were insoluble at $36\text{--}37^\circ\text{C}$ (Figure 5).

Measurement of pH in Mixtures

Table 2 shows the pH values of each non-particulate steroid and local anesthetic. All non-particulate steroids were basic, BSP was the most basic (pH 8.5), and local



Figure 4 Microscopic findings of dexamethasone palmitate (DPA) mixed with 0.75% ropivacaine HCl (ropivacaine) ($\times 100$).



Figure 5 Insoluble particulates after heating ($36\text{--}37^\circ\text{C}$) ($\times 400$). These particulates were produced from betamethasone sodium phosphate (BSP) mixed with 0.75% ropivacaine HCl (ropivacaine).

Table 2 The pH of Non-Particulate Steroids, Normal Saline, and Local Anesthetics

Non-Particulate Steroids and Local Anesthetics	pH
Betamethasone sodium phosphate 5.2 mg/mL	8.5
Dexamethasone disodium phosphate 4 mg/mL	7.6
Dexamethasone palmitate 5 mg/mL	7.1
0.75% ropivacaine HCl	6.1
0.75% levobupivacaine HCl	5.8
0.5% bupivacaine HCl	6.4
1% lidocaine HCl	6.3

anesthetics were acidic; levobupivacaine was the most acidic (pH 5.8). Other local anesthetics showed a pH of < 7.0.

The mixture of BSP and normal saline showed a pH of 7.83 (Table 3). BSP and ropivacaine had pH values between 6.46 (1:3 ratio) and 7.01 (1:1 ratio). BSP and levobupivacaine had the most acidic mixture (pH 6.13–6.92). BSP and bupivacaine or lidocaine were close to neutral pH. The mixture of BSP with local anesthetics was more acidic when higher ratios of local anesthetics were used in the mixture.

All mixtures of DSP and normal saline or local anesthetics tended to be more acidic than similar mixtures with BSP (rather than DSP). DSP and normal saline had pH values between 6.94 (1:3 ratio) and 7.12 (1:1 ratio). DSP and ropivacaine, levobupivacaine, bupivacaine, and lidocaine had a pH of 6 to < 7. Additionally, the mixture of DSP with local anesthetics was more acidic when higher ratios of local anesthetics were used in the mixture. DPA and local anesthetics produced the most acidic mixtures. DPA and normal saline had pH values between 6.14 (1:3 ratio) and 6.42 (1:1 ratio). The most acidic mixtures, DPA and levobupivacaine, had a pH < 5.

Discussion

In our study, non-particulate steroids could form crystals depending on which local anesthetic they were mixed with. Only lidocaine and all non-particulate steroids did not produce any identifiable crystals. Furthermore, DPA and all local anesthetics did not form substantial crystals. However, when ropivacaine and levobupivacaine were mixed with BSP or DSP, crystals of various shapes and sizes were formed. Among the non-particulate steroids, ropivacaine or levobupivacaine, and BSP formed the largest crystals. Additionally, these crystals were insoluble upon heating at 36–37 °C.

Table 3 Measurement of pH in Mixed Solutions (Normal Saline or Local Anesthetics and Non-Particulate Steroids)

Non-Particulate Steroids	Normal Saline or Local Anesthetics	Dilution	pH
Betamethasone sodium phosphate 5.2 mg/mL	0.9% Normal saline	1:1	7.83
		1:2	7.83
		1:3	7.83
	0.75% ropivacaine HCl	1:1	7.01
		1:2	6.62
		1:3	6.46
	0.75% levobupivacaine HCl	1:1	6.92
		1:2	6.35
		1:3	6.13
	0.5% bupivacaine HCL	1:1	7.41
		1:2	7.23
		1:3	7.11
1% lidocaine HCl	1:1	7.31	
	1:2	7.16	
	1:3	7.03	
Dexamethasone disodium phosphate 4 mg/mL	0.9% Normal saline	1:1	7.12
		1:2	6.95
		1:3	6.94
	0.75% ropivacaine HCl	1:1	6.66
		1:2	6.45
		1:3	6.32
	0.75% levobupivacaine HCl	1:1	6.53
		1:2	6.33
		1:3	6.23
	0.5% bupivacaine HCL	1:1	6.79
		1:2	6.67
		1:3	6.59
1% lidocaine HCl	1:1	6.57	
	1:2	6.38	
	1:3	6.22	
Dexamethasone palmitate 5 mg/mL	0.9% Normal saline	1:1	6.42
		1:2	6.21
		1:3	6.14
	0.75% ropivacaine HCl	1:1	5.4
		1:2	5.21
		1:3	5.08
	0.75% levobupivacaine HCl	1:1	4.87
		1:2	4.71
		1:3	4.65
	0.5% bupivacaine HCL	1:1	5.17
		1:2	5.11
		1:3	5

(Continued)

Table 3 (Continued).

Non-Particulate Steroids	Normal Saline or Local Anesthetics	Dilution	pH
	1% lidocaine HCl	1:1	5.36
		1:2	5.46
		1:3	5.51

There has been a discussion on safety regarding the use of particulate steroids for TFESI. Rare catastrophic complications after TFESI have been attributed to particulate steroids, including suggestions that the particulate steroid itself could serve as emboli.^{7–9} The vessel dimensions of the microvascular system vary in size: capillary, 5–8 μm ; arteriole, 10–15 μm ; metarteriole, 20–50 μm ; artery, >50 μm .¹¹ The grouping of particulate sizes in this study was set as a reference for the vessel dimensions of the microvascular system. If particulate steroids, or mixtures of steroids and local anesthetics, were injected into the microvascular system, crystals of >50 μm may play the role of artery emboli.

Benzon et al¹⁵ reported the size of crystals formed upon mixing particulate steroids with local anesthetics (1% lidocaine) or normal saline, using the following groups: 0–20, 21–50, 51–1000, and >1000 μm . Particulate sizes of particulate steroids were concentrated in the range of 0–1000 μm . Particulate sizes >1000 μm were reported, although there were very few of these. In our study, when ropivacaine or levobupivacaine and BSP were mixed, the size of the resulting crystals was smaller (0–500 μm or greater) than that during mixing of particulate steroids in a previous report (0–1000 μm). However, small-sized crystals may be potential emboli of vessels. Thus, mixtures of ropivacaine or levobupivacaine and BSP may exhibit a risk similar to that of particulate steroids. Crystals of sizes –51–100 μm or >100 μm were observed only in mixtures of BSP and ropivacaine or levobupivacaine. Crystals > 500 μm in size were observed only in the mixture of ropivacaine and BSP, but there were no crystals >1000 μm in size (Figure 2B and D).

In previous studies, when local anesthetics (ropivacaine, bupivacaine, lidocaine) and DSP or BSP were mixed, crystal production was reported.^{16,17} Alkalization has been suggested as the cause of crystals in mixtures of local anesthetics and non-particulate steroids.¹⁷ In our study, all local anesthetics were acidic (pH < 7.0), and non-particulate steroids were basic (DSP, pH 7.6) or strong basic (BSP, pH 8.5). The more basic steroids (BSP, pH 8.5 > DSP pH 7.6 > DPA pH 7.1) tended to produce more

crystals. For the same steroid (except DPA), crystal formation was the greatest for ropivacaine (pH 6.1), followed by levobupivacaine (pH 5.8) and bupivacaine (pH 6.4), with non-particulate steroids. Additionally, lidocaine (pH 6.3) did not form crystals with any of the steroids used in this study. A higher fraction of local anesthetic in all mixtures was associated with lower pH, but did not significantly affect the number of crystals. Thus, alkalization of steroids may be more important than the local anesthetic pH in the process of crystal formation.

We used BSP in this study. However, BSP/betamethasone acetate (Celestone Soluspan[®]; Schering-Plough, Kenilworth, NJ) as a compound drug has been used in the USA Only BSP is available as a cream in the USA or it can be ordered separately from compounding companies. This compound drug has a long-acting duration, although BSP alone (non-particulate, pure liquid) is a short-acting drug. This compound may be preferred for use in clinical settings because of its long-acting duration; however, it has inherent issues, such as potency, accuracy, and sterility. The results of the present study suggest that clinicians should be careful while selecting local anesthetics when they use BSP with local anesthetics; therefore, more attention should be paid to the use of compound drugs with local anesthetics.

DPA, which was used in this study, is not commonly used for an epidural injection, and its safety remains unclear. It is an injectable lipid emulsion, and dexamethasone with lipid microspheres. DPA may not be expected to act as an embolus because the average liposome diameter of DPA is 0.1–0.3 μm , but its safety should be demonstrated.^{18,19} We measured the pH of DPA, and found that it was pH 7.1. Other non-particulate steroids were basic (DSP, pH 7.6) or strong basic (BSP, pH 8.5), whereas DPA was near neutral. When DPA (pH 7.1) and local anesthetics (pH < 7.0) were mixed, the pH of the resulting mixtures was acidic. Based on our findings, alkalization of steroids may affect crystal formation. It is thought that the almost neutral pH of DPA does not form crystals when mixed with local anesthetics. DPA 4 mg has a potency equivalent to that of DSP (2.5 mg). Thus, DPA exhibits potency that is one-half to one-fifth that of DSP. DPA can be mixed with local anesthetics (ropivacaine, levobupivacaine, bupivacaine, or lidocaine) without the risk of crystal formation. DPA in the clinical setting has been used for intra-articular injection in arthritis patients; it has also been used to treat arthritis in animal models.^{20,21} Although there have been no reports of epidural steroid injections for spinal pain, their use in lumbar

facet joint injections has been reported.²² DPA should be tested for safety to enable its use in the epidural space.

On the basis of the results of this study, the mixture of ropivacaine or levobupivacaine and BSP may be discontinued for TFESI. The use of mixtures of ropivacaine or levobupivacaine and DSP may be possible because these mixtures produced very small crystals. Among the local anesthetics, lidocaine or bupivacaine is recommended when mixed with non-particulate steroids, as neither of them rarely form crystals. Studies have compared the effectiveness of particulate and non-particulate steroids for spinal injection through the transforaminal route.^{23–26} Physicians believe that particulate steroids have a longer duration than non-particulate steroids. However, these studies showed that the difference in effectiveness was neither clinically nor statistically significant. In addition, many studies have shown that injection of local anesthetics alone is sufficient for pain relief instead of combining corticosteroids with local anesthetics.^{27,28} Notably, non-particulate steroids are safer substitutes, but caution should be exercised in the selection of local anesthetics based on the results of this study.

We have specific recommendations for the use of non-particulate steroids with local anesthetics in TFESI: ropivacaine or levobupivacaine and BSP may be discontinued in ESI; ropivacaine or levobupivacaine, and DSP may be used because their mixture generated very small particulates; lidocaine or bupivacaine as local anesthetics are recommended; DPA may be optimal, but additional studies regarding its safety and effectiveness are needed. However, the ESI regimen varies, and there are no guidelines that suggest that local anesthetics must always be used. These recommendations are only relevant if mixtures of local anesthetics and non-particulate steroids are used in TFESI.

This study has some limitations. First, we thought that alkalization of steroids may play a more important role in the process of crystal formation. However, further research is needed to determine the exact cause. Second, the characteristics of other formulations can be different, although the local anesthetics and non-particulate steroids used in this study were the same ingredients. We cannot generalize this result for all other marketed formulations. Third, the concentration of the local anesthetic agent used for our experiment was higher than its concentration used for an epidural block. We only changed the volume of the local anesthetic without using normal saline. The crystal formation may be different with varying concentrations of local anesthetic. Fourth, we attempted to melt the crystals from

all mixing regimens at 36–37 °C. and all crystals were insoluble at 36–37 °C. This is consistent with previous reports.^{17,29} However, because an in vivo analysis was not performed, it is unclear whether crystals may dissolve during actual ESI procedures. In addition, we could not prove the safety (eg, neurotoxicity and role of emboli) of these crystals when they reach the arterial supply to the spinal cord or brain during procedures.

Conclusion

In conclusion, non-particulate steroids have been thought to be safer than particulate steroids because of previous catastrophic embolic events in ESI, especially TFESI, which resulted from particulate steroid usage. However, because some non-particulate steroids can form particulates when mixed with local anesthetics, these combinations should be avoided. Mixtures of non-particulate steroids with local anesthetics that do not form crystals or form less of them are recommended.

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