Basic Science

Microscopic Study of Injectable Steroids: Effects of Postmixing Time on Particle Aggregation

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Background: Epidural steroid injection (ESI) is a common practice for pain treatment since 1953. In 2014, the FDA issued a warning about ESI. Studies have focused on the effect of the particle size and their ability to generate harmful aggregates. Although steroid aggregates provide longer times for reabsorption, therefore a longer anti-inflammatory effect, they are potentially harmful to the central nervous system via embolic mechanisms.

Previous studies have established that steroidal aggregates with asizes over 100 µm are potentially able to occlude blood vessels. Studies by Tiso et al and Benzon et al addressed the role of steroids on CNS adverse events, with similar outcomes. The main difference was on the role of aggregates with a size over 100 µm, which Benzon et al. attributed to the ability of certain steroid preparations to rapidly precipitate and form large aggregates.

Objectives: Studying the effect of the time elapsed between mixing the steroid preparation and injection on the number and size of aggregates with sizes above 100 µm.

Study Design: Original study in basic science.

Setting: Basic science

Methods: Steroids evaluated are commonly used in Spain for ESI: betamethasone, triamcinolone, and dexamethasone. The size and number of the aggregates was determined for undiluted commercial steroid preparations in the usual amount for a single and double dosage used for ESI.

Samples were examined with a Leica TCS-SP2 microscope at the first, the fifth and the 30th minute after shaking the preparations. Aggregates observed in the different preparations were manually counted and grouped in the following size range: 0-20, 20-50, 50-100, 100-300, 300-500 and > 500 µm.

Statistical analysis was carried out using the R software. Nonparametric techniques were used in the comparison of aggregate size. Global comparison of the groups using the Kruskal-Wallis test and post-hoc comparisons using the Wilcoxon test, adjusting *P*-values by the Holm method for multiple comparisons

Results: Aggregates present in triamcinolone and betamethasone samples were statistically larger than in dexamethasone samples. Triamcinolone suspensions produced significantly larger aggregates than betamethasone five minutes after mixing. Triamcinolone preparations produced greater particle aggregates (> 500 µm), which were not present in dexamethasone and betamethasone preparations.

Limitations: Study how the human internal factors like blood elements and spinal fluid could interact with steroids and influence the size of the aggregates formed.

Conclusions: This study demonstrates that the size of the particles injected depends on the type of steroid and the time allowed between mixing and injecting. The results demonstrate that waiting longer than 5 minutes between mixing and injecting can predispose the formation of potentially harmful aggregates in triamcinolone and betamethasone samples. The presence of greater particle aggregates (> 500 µm) may occlude some important vessels and arteries with serious adverse results. Vigorous shaking of the injectable could prevent such events.

Key words. Epidural steroid injection. Triamcinolone. Betamethasone. Dexamethasone. Steroid aggregates.

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Epidural steroid injection has been a common practice for back, neck, and radicular pain treatment since Lievre et al (1,2) reported the first use for this purpose in 1953. Interlaminar, caudal, and transforaminal injections have been the most common approaches in pain management units.

On April 23, 2014, the US Food and Drug Administration (FDA) issued a letter warning that injection of steroids into the epidural space may result in rare but serious adverse events, including "loss of vision, stroke, paralysis, and death" (3). Specifically, the FDA report includes 15 cases of adverse events in the central nervous system (CNS) because of the use of particulate steroids injections in the epidural space. Forty percent (6/15) of these events were related to cervical transforaminal approach, 26% (4/15) to lumbar transforaminal procedures, 6% (1/15) to thoracic interlaminar injections, and 12% (2/15) to cervical interlaminar epidural approaches, whereas the other 12% (2/15) were not related to epidural procedures (cervical paravertebral block and C1-C2 facet joint injection).

The FDA warning generalized and extrapolated all the complications reported through several years, but did not differentiate between the formulation used, the approach adopted, and in which level of the epidural space the infiltration was done.

Different studies have focused on the potentially harmful effects of the size of the aggregates present in the steroid's preparations. Potential mechanisms postulated in relationship to these CNS adverse events are diverse (4-16) and include arterial damage because of the needle (17), vasospasm phenomena (18), and embolic phenomena (8).

Although particle aggregation provides steroids a longer time for reabsorption, the resulting aggregates could be harmful in the CNS via embolic mechanisms (4-18).

Anatomic studies (24-26) have been performed around the size of the vessel and the potential effect of arterial occlusion due to an embolic event. Based on those studies, aggregates between 100 and 1000 μm could potentially occlude vessels with dangerous effects.

Despite the existence of several studies around this topic (8,20,21), there are still questions related to the nature of the steroid, components, and how they carry out their adverse effects. The foremost studies on this topic were those carried out by Tiso et al (8) and Benzon et al (20). Although results were similar in both there were some capital differences between them. First, Benzon et al (20) noted that preparations of dexamethasone and betamethasone sodium phosphate were free of aggregates, whereas Tiso et al (8) found small aggregates in these preparations. Second, Tiso et al (8) did not account for aggregates larger than 50 μm, reporting "particle size approached 100 μm in some cases," whereas Benzon et al (20) reported aggregates larger than 1,000 μm. Benzon et al (20) attributed these differences to the rapid ability of these preparations to precipitate and form large aggregates. Despite both studies having similar outcomes, there are important differences, especially regarding aggregates larger than 100 μm. Furthermore, the effect of the time elapsed after mixing or dilution on the size and amount of particle aggregates was not established.

Although the causes of the differences between Tiso et al (8) and Benzon et al (20) studies remain unclear, aggregation of steroid aggregates during the time elapsed after mixing or dilution could be a reason. The objective of this study was to measure the effect of the time elapse between mixture and injection on particle aggregation and its presence in the different steroid preparations commercially available in Spain. This was measured for undiluted and diluted preparations under conditions commonly used in clinical practice.

Methods

The steroids evaluated are commonly available and used in Spain for epidural injections. These are Celestone Cronodose (betamethasone 5.7 mg/mL; Merck, Sharp, and Dohme [Merck Sharp & Dohme Corp, Kenilworth, NJ], SA), each mL contains 3.9 mg of betamethasone disodium phosphate and 3 mg of betamethasone acetate; Trigon Depot (40 mg/mL; Bristol-Myers Squibb [Bristol-Myers Squibb Company, New York, NY], SA) each mL contains 40 mg of triamcinolone acetate; and Fortecortin (4 mg/mL; ERN Laboratories [ERN Laboratories, Barcelona], SA) each mL contains 4 mg of dexamethasone disodium phosphate.

The size of the aggregates were determined and compared for different samples, consisting of undiluted commercial steroid preparations in the usual amount used for epidural injections: single and double dosage (4 or 8 mg of Fortecortin, 6 or 12 mg of Celestone, 40 or 80 mg of Trigon).

Samples were prepared following the usual clinical practice. Steroids vials were kept below 25ºC. Before evaluation, the steroid vial was shaken 20 times (FDA recommends shaking it before use but has not stated

how many times). After shaking, 1 mL of the preparation was drawn using a 19-gauge needle, and a drop was placed on a microscope slide and covered immediately with a coverslip.

Samples were examined with a Leica TCS-SP2 microscope (Leica Microsystems, Heidelberg GmbH, Mannheim, Germany). Five images were collected from each sample from the most representative areas at 1, 5, and 30 minutes after the collection. These times represent usual times between mixing/dilution and injection.

Pictures were analyzed with the GIMP program (Licensed under a Creative Commons Attribution-ShareAlike 4.0 International License). The aggregates observed in the different preparations were manually measured and grouped in the following size range: 0–20, 20–50, 50–100, 100–300, 300–500, and > 500 µm.

We established 100 µm as the maximum aggregate size to cause vessel obstruction, as it is known that aggregates larger than 100 µm may lead to this (24).

Statistical analysis was carried out using the R software (The R Foundation). Data were grouped by time to compare particle size for each corticosteroid at 1, 5, and 30 minutes. Exploratory data analyses were performed using sample percentiles, interquartile ranges, and boxplot diagrams. Nonparametric techniques were used in the comparison of the particle size; in particular, the global comparison of the groups was performed by the Kruskal–Wallis test and post hoc comparisons using the Wilcoxon test, adjusting the *P* values by the Holm method for multiple comparisons. All statistical methods were performed with a level of significance $\alpha = 0.05$, considering the results with an adjusted $P < 0.05$ as statistically significant.

Results

Comparisons by Time in Undiluted Samples

Table 1 shows the total number of aggregates counted in undiluted samples of the 3 corticoids studied. It also shows the percentage of aggregates with sizes above 100, 300, and 500 µm. Figure 1 and Table 2 show median values of the number of particle aggregates with size above 100 µm as a function of time elapsed (1, 5, and 30 minutes) after shaking undiluted samples. Table 3 shows the *P* values for paired comparisons of the mean values of aggregates with a size above 100 µm.

Measurements 1 Minute After Shaking

Undiluted triamcinolone samples contained approximately 4,000 aggregates. Only 1.43% of these were larger than 100 µm, and only 0.14% larger than 300 µm. There were no aggregates with a size above 500 µm. Undiluted betamethasone samples contained approximately 2,400 aggregates, with 0.97% of these larger than 100 µm. It is important to note that there were no aggregates measuring 500 µm or larger. Undiluted dexamethasone samples measured 1 minute after shaking contained the smaller number of aggregates among the 3 preparations (approximately 830 particles) and none of them were larger than 100 µm.

The differences in the number of aggregates between dexamethasone and triamcinolone and between dexamethasone and betamethasone were statistically significant, but the difference between betamethasone and triamcinolone samples was not statistically significant.

Table 1. *Total number of aggregates counted in undiluted samples of the 3 corticoids studied.*

Steroid	Time (min)	Number of Aggregates	> 100 µm (%)	> 300 µm (%)	> 500 µm (%)
Triamcinolone	1	4,035	1.43	0.14	0
	5	11,725	1.96	0.55	0.06
	30	10,870	2.41	0.81	0.18
Dexamethasone	1	826	0	0	0
	5	3,434	0.03	0	0
	30	3,082	0.19	0	0
Betamethasone	1	2,368	0.97	0	0
	5	11,960	0.59	0	0
	30	16,662	2.14	0.32	0.07

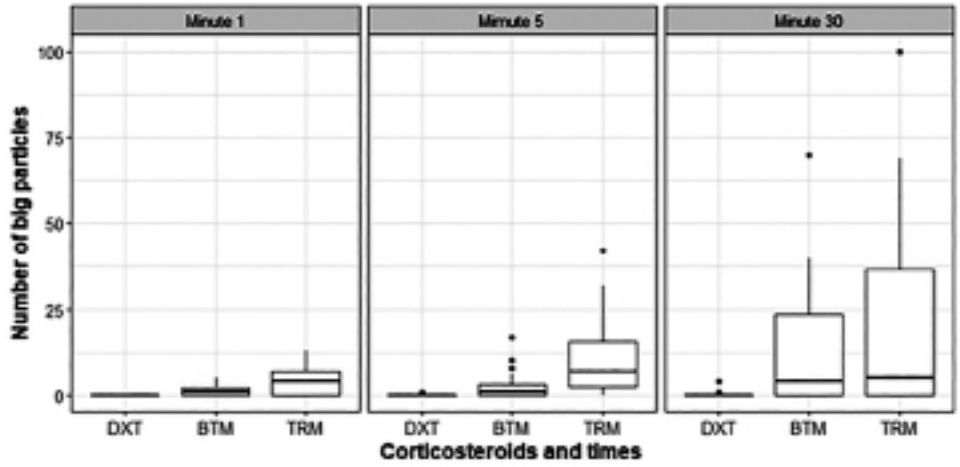

Fig. 1. *Median values of the number of particles aggregate with size above 100 μm as a function of time elapsed (1, 5, and 30 minutes) after shaking undiluted samples*

Table 2. *median values of the number of particles aggregate with size above 100 μm as a function of time elapsed (1, 5, and 30 minutes) after shaking undiluted samples*

	1 Minute		5 Minutes		30 Minutes	
Steroid	Median	IQR	Median	IQR	Median	IQR
Dexamethasone	0	0	0	0	0	0
Betamethasone	1	2	1	3	4	23.50
Triamcinolone	4	7	7	13	5	

IQR, interquartile range.

Table 3. *P values for paired comparisons of the mean values of aggregates with a size above 100 μm.*

Comparison	1 Minute	5 Minutes	30 Minutes
Dexamethasone vs. Betamethasone	0.001	< 0.001	< 0.001
Dexamethasone vs. Triamcinolone	< 0.001	< 0.001	< 0.001
Betamethasone vs. Triamcinolone	0.118	0.002	0.728

Measurements 5 Minutes After Shaking

Undiluted triamcinolone samples 5 minutes after shaking contained approximately 11,750 aggregates. We found 230 aggregates with size above 100 μm (1.96% from the total), 64 aggregates above 300 μm (0.55%), and 7 aggregates above 500 μm. A similar number of aggregates were counted in undiluted betamethasone (approximately 12,000 aggregates). Out of these, 71 aggregates (0.59%) had sizes above 100 μm, whereas none were found above 300 μm. In undiluted dexamethasone samples, we counted approximately 3,450 aggregates, but only 1 aggregate (0.03%) was larger than 100 μm and no aggregates were larger than 300 μm in these samples. The differences in the number of aggregates with size above 100 μm between the 3 undiluted corticoids were statistically significant.

In general, the number of large aggregates observed at 5-minute preparations was larger than that observed in samples at 1 minute. These aggregates tend to deposit at the bottom of the flask (the deposit zone), especially in particulate steroids (betamethasone and particularly triamcinolone).

Large aggregates (between 300 and 500 μm) were frequently present in triamcinolone samples 5 minutes after shaking. These large aggregates were isolated on the bottom of the flask. In contrast, aggregates over 300 μm were not isolated from the betamethasone and dexamethasone samples.

Measurements 30 Minutes After Shaking

Undiluted samples of triamcinolone contained approximately 10,900 aggregates 30 minutes after shaking. We found a total of 261 aggregates with size over 100 µm (2.41% from the total), 88 aggregates over 300 µm (0.81%), and 20 aggregates over 500 µm (0.18%). It is important to stress that in some cases we could not differentiate accurately the size of the aggregates. The size of such aggregates, particularly in triamcinolone samples, was so large that it was beyond the intervals fixed. The number of aggregates in the undiluted betamethasone samples was approximately 16,700. Out of these, 356 aggregates had sizes over 100 µm (2.14% from the total), 53 over 300 µm (0.32%), and 12 aggregates over 500 µm (0.07%). In contrast, samples of undiluted dexamethasone contained approximately 3,100 aggregates, with only 0.19% of these larger than 100 µm. No aggregates were larger than 300 µm.

Statistical comparisons of the results obtained among the undiluted samples measured 30 minutes after shaking indicate that there are significant differences between dexamethasone and the other 2 corticosteroids. Although the number of aggregates larger than 100 µm present in betamethasone preparations was higher than in triamcinolone preparations, the difference between them was not statistically significant.

Discussion

CNS complications due to epidural particulate steroid injections are rare considering its extended use for many years. In April 2014, the FDA issued a warning citing 15 cases of CNS adverse events because of the use of particulate steroids injections in epidural space (3). Forty percent (6/15) of these events were related to a cervical transforaminal approach, 26% (4/15) to lumbar transforaminal procedures, 6% (1/15) to thoracic interlaminar, and 12% (2/15) to cervical interlaminar epidural approaches, whereas the other 12% (2/15) were not related to epidural procedures (one was a cervical paravertebral block and the other a C1-C2 facet joint injection). The FDA warning, however, did not differentiate between the type of steroid and the diluent used and the vertebral level treated.

It is well known that the epidural space is diverse, presenting variations among vertebral levels (cervical, thoracic, lumbar, and caudal) and even between patients. These variations and specific conditions bound adverse events on the different levels treated. Some vascular structures, such as the vertebral artery and the artery of Adamkiewicz, are close to the epidural space and some approaches involve important risks against those with serious implications. It is therefore indispensable to know anatomic pathways very well to assure safe procedures.

Several mechanisms could be potentially responsible for CNS complications (8-17,20-25). Ischemic phenomena owing to embolism of the particulate steroid is a possible cause, as well as arterial spasm (18), arterial injury, and proximal or intraneural spread of the injected medications (8,16,17).

Ischemic phenomena are less likely to happen at some vertebral levels and under specific approaches. Lumbar segments below L3, caudal and interlaminar approaches could be considered safe. In those situations, vascular structures will be located far enough away to avoid serious damage. Perhaps injection in some vertebral levels (such as cervical) and some approaches (such as transforaminal) are particularly risky because of the proximity of essential vascular structures, in which damage could lead to serious events. For such reasons, the use of particulate steroids should be considered on an individual basis.

Several anatomic studies (24-26) have established that steroidal aggregates with sizes over 100 µm are potentially able to occlude, at least partially, some blood vessels. Tiso et al (8), as well as Benzon et al (20), carried out the main studies addressing the role of steroids on CNS adverse events. Tiso et al (8) focused on the aggregation of injectable particulate steroids (triamcinolone and methylprednisolone) and how these can yield aggregates over 100 µm, which may contribute to microvascular "sludging" and subsequent occlusion/infarction. Benzon et al (20) determined the size of aggregates in undiluted steroids and diluted preparations with local anesthetic and saline solutions.

Although both studies had similar outcomes, there were important differences between them. Tiso et al (8) found small aggregates in preparations of dexamethasone sodium phosphate or betamethasone sodium phosphate, whereas Benzon et al (20) noted that these were free of aggregates. More relevant to our study, Tiso et al (8) reported the presence of a low number of aggregates with sizes approximately 100 µm, whereas the size of the aggregates reported by Benzon et al (20) were, in some cases, larger than 1,000 µm. Benzon et al (20) attributed these differences to the rapid ability of these preparations to precipitate and form large aggregates.

Until now, these differences have remained unexplained. To interpret the differences reported in the

aforementioned studies, our investigation focused on studying the effect of the time elapsed between shaking/mixing and injection on the size of the aggregates.

Our results demonstrate that allowing mixtures of betamethasone or triamcinolone to rest for more than 5 minutes between the time of mixing and injection can predispose the formation of large particle aggregates (> 100 μm) with the potential for dangerous outcomes.

We observed that preparations examined after the first minute of shaking/mixing barely presented aggregates over 100 μm. Such aggregates were found only in triamcinolone and betamethasone preparations, but always in low proportion, accounting for approximately 1.4% of all aggregates in triamcinolone preparations and about 1% in betamethasone preparations. At this short mixing-to-injection time, aggregates sized over 300 μm were found only in triamcinolone preparations, although in a particularly small amount (0.14% from the total) and were nonexistent in preparations of the other steroids. As the time after shaking increased, the size and the number of the aggregates measured also increased. The effect was found to be more pronounced in triamcinolone preparations, in which at 5 minutes after shaking the aggregates over 100 μm represent approximately 2% of the total, and at 30 minutes, they were approximately 2.4%. Similarly, the amount of aggregates with size above 300 μm in triamcinolone samples increased from 0.14% of the total at 1 minute after shaking to 0.5% and 0.8% at 5 and 30 minutes after shaking, respectively. The effect of time on aggregation was also evident in betamethasone preparations, in which the percentage of aggregates larger than 100 μm increased from 0.6% at 5 minutes after shaking to 2.1% at 30 minutes after shaking.

In contrast to triamcinolone preparations, aggregates larger than 300 μm in betamethasone preparations were only observed after 30 minutes and represented only 0.32% of the aggregates. Finally, particularly large aggregates (over 500 μm) represented a relatively low percentage of the total and were not observed after 1 minute post-shaking. In triamcinolone preparations, they were 0.06% at 5 minutes after shaking and had increased to 0.18% at 30 minutes. In contrast, these particularly large aggregates were only observed in betamethasone preparations that have stood for 30 minutes after shaking.

It is evident from our results that, in general, triamcinolone preparations tend to produce a large number of aggregates in comparison to the other steroids studied.

We have demonstrated the impact of the resting time between mixture and injection of the sample and how this can predispose the formation of large aggregates (especially in triamcinolone samples).

Although both betamethasone and triamcinolone are particulate steroids, the aggregates formed in betamethasone preparations are smaller than those formed in triamcinolone preparations under similar conditions. These results agree with those reported by Benzon et al (20). Furthermore, we did not find any particle larger than 300 μm in betamethasone samples after 1 or 5 minutes of mixing. In contrast, triamcinolone preparations were more likely to have particularly large aggregates (> 500 μm). The presence of such large size aggregates in triamcinolone preparations was frequent after 5 and 30 minutes of mixing.

The presence of these particularly large aggregates mostly occurred at the bottom of the flask rather than at the surface, indicating that further coalescence of such aggregates would precipitate them out of the particulate suspension. Vigorous shaking of these preparations before injection could disaggregate large particulates that have been formed during the waiting time. However, recent studies by Laredo et al (28) in an animal model indicate that triamcinolone (as well as prednisolone and methylprednisolone) induces the agglutination of red blood cells, which have been transformed into spiculate cells on the injection of the steroid in the artery. Therefore the practice of injecting triamcinolone preparations under conditions that produce large aggregates should be avoided.

Our results show that the presence of aggregates larger than 500 μm was minimal in betamethasone preparations and nonexistent in dexamethasone preparations. Indeed, dexamethasone preparations did not show any large aggregates after 30 minutes of mixing, which is a significant differentiating factor when compared with both betamethasone and triamcinolone preparations.

The benefits granted by corticosteroids via epidural injection for the treatment of radicular pain are well documented. The expansion of their use for this purpose during several years has resulted in an increase in the number of complications that may be related to their use. The mechanisms that produce damage in the CNS can be multiple and must be demonstrated by anatomic and experimental studies to improve therapy protocols and reduce risk.

Conclusions

There is no evidence indicating that particulate steroids are better in relieving pain compared with their nonparticulate counterparts (29). Our results imply that it is prudent to use nonparticulate steroids, such as dexamethasone, as they may provide a benefit at minimum risk in contrast to using particulate steroids, and in particular triamcinolone. At the very least, the dangers and alternatives should be flagged within the patient group as part of a shared decision-making process.

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