FACTFINDERS FOR PATIENT SAFETY

STEROID INJECTIONS AND HYPERGLYCEMIA IN DIABETES MELLITUS TYPE 2

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MYTH: Corticosteroid injections are contraindicated in the setting of hyperglycemia or suboptimally controlled Diabetes Mellitus Type 2 (DM2).

FACT: Corticosteroid injections can safely be administered to patients with DM2 in most cases, including those with suboptimal management. Because there is a risk of hyperglycemia and related complications in these patients, a trial of conservative care before proceeding with a steroid injection is optimal. Patients with DM2 should be counseled on the signs, risks, and sequelae of hyperglycemia in the post-injection period and appropriate steps to take if significant hyperglycemia occurs.

Diabetes Mellitus Type 2 (DM2) has an enormous burden on healthcare systems around the world, and prevalence is rising [1,2]. Physicians performing corticosteroid injections will invariably care for patients with DM2. There are many potential complications related to hyperglycemia [3]. Acute complications of hyperglycemia include diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) [4]. Patients with DM2 are at risk for DKA and HHS, which can result in potentially life-threatening metabolic and visceral organ complications [5,6]. Risk factors for the development of DKA or HHS are poor medication compliance, infection, and exogenous corticosteroid administration [5,6,7], especially when the time between doses is reduced [8].

Assessing for Hyperglycemia Before Injection

Direct measurements of hyperglycemia leading to a diagnosis of DM2 include a fasting blood glucose ≥126 mg/dL, a glucose level of ≥200 mg/dL at 2 hours following ingestion of 75 g glucose in an oral glucose tolerance test (OGTT), or a random blood glucose ≥200 mg/dL; however, these values may not correlate with one another [9]. Though blood glucose levels are often used, the substantial postprandial and daily rhythmic variability undermines the reliability of this testing [10].

There may be some value to frequent blood glucose measurements in those at risk for corticosteroid-induced hyperglycemia [9]. Other tests, including hemoglobin A1C [9] and fructosamine [11], appear to be of little value in this setting. Unfortunately, no reliable point-in-time quality measurement to assess the risks of corticosteroid-associated hyperglycemia exists to guide the safety of the injection.

Intra-articular and Periarticular Steroid Injections and Hyperglycemia

A rise in blood glucose levels following intra-articular corticosteroid injection in patients with diabetes mellitus has been well-documented [12-14]. Steroid-induced hyperglycemia can occur anywhere from a few hours to days after a corticosteroid injection and may have a greater effect on postprandial blood glucose levels than fasting blood glucose levels [1,14-16].

A 2016 systematic review analyzed seven studies with a total of 72 patients with diabetes who underwent intra-articular corticosteroid injections in the shoulder, elbow, knee, or ankle joint [14]. A variety of corticosteroids, including methylprednisolone acetate, triamcinolone acetonide, betamethasone acetate/betamethasone sodium phosphate, and triamcinolone hexacetonide, in doses ranging from 35 mg to 80 mg of equivalents of methylprednisolone, were used across the studies. Increases in blood glucose levels were seen in all studies, and were considered "substantial" in four studies. The highest value reported was 500 mg/dL. The timing of the peak increase following intra-articular injection was highly variable, ranging from 48 hours to 7 days following injection, and occurring most frequently within 24 to 72 hours following injection. Overall, while studies vary in the timing of blood glucose checks and follow-up duration, there is strong evidence of statistically significant increases in glucose levels. None of the studies indicated any postinjection glycemic complications, though subjects reportedly had well-controlled diabetes.

Another study followed 25 patients with non-insulin-dependent DM2 who were connected to a continuous glucose monitoring system. These patients received 40 mg of methylprednisolone acetate administered to the subacromial space, glenohumeral space, or acromioclavicular joint [17]. Data were collected from 3 days before through 11 days after the corticosteroid injection. There was a statistically significant but relatively mild increase in mean glucose level in the first 3 days after the injection. However, new-onset severe hyperglycemia (glucose levels of greater than 350 mg/dL) was found in 4 of 25 patients during the early post-injection period. Two of the four patients with new-onset severe hyperglycemic levels had baseline A1c levels of 7.4% and 6.8%, demonstrating that severe hyperglycemia can occur in patients with moderately controlled A1c. The glycemic changes were limited to 2-3 days after the injection. No subjects reported adverse effects related to the injection, nor were there changes to antihyperglycemic treatment after the injection.

A subsequent study followed 51 patients with DM2 who received either subacromial subdeltoid bursa or shoulder joint injections of 20 or 40 mg triamcinolone (N=22) or lumbar transforaminal epidural corticosteroid injection and/or medial branch block with 10 mg dexamethasone or 20 mg dexamethasone plus 40 mg triamcinolone (N=29) [18]. Blood glucose was significantly (p=0.012) elevated by 64.0±29.4 mg/dL, compared to baseline at 1 day after corticosteroid injection, which reverted to baseline levels 2 days after injection. Higher HbA1c level (>7%) before injection was significantly (p=0.003) associated with the degree of blood glucose increase 1 day after injection. Age, sex, DM duration, body mass index, concurrent diagnosis of hypertension, insulin use, injection site, or corticosteroid dose did not significantly affect blood glucose after corticosteroid injection, though the study population was small, limiting the power of the study. Though the study did not evaluate differences as they relate to the site of corticosteroid administration and resultant hyperglycemia, there was no report of severe hyperglycemia resulting in complications in this cohort.

Lumbar ESI and Hyperglycemia in Diabetics

Epidural administration of corticosteroids has been shown to cause an increase in blood glucose levels in diabetics in several small studies.

- Gonzalez *et al.* [19] prospectively observed 12 patients with diabetes (6 non–insulin–dependent and 6 insulin-dependent, DM1 vs DM2 was not specified) who received lumbosacral or caudal epidural injections with betamethasone ranging from 12 to 18 mg. Blood glucose levels peaked on the day after the injection (236 mg/dL (207-265) p=.0001), had a significant elevation up to the second day after the injection (160 mg/dL (130-191) p=.03), but remained elevated in the three days after the injection.

- Chuatatape *et al.* [20] prospectively studied a group of six diabetic (median A1C of 6.5, DM1 vs DM2 was not specified) and 12 non-diabetic patients who received dexamethasone 8 mg into the epidural space. Fasting blood glucose levels were significantly higher on day one post-procedure [6.3 mmol/L compared to the baseline level of 5.3 mmol/L (p=0.026)] but not at 7 or 21 days after the procedure in all subjects. A separate analysis to ascertain the differences between diabetic and non-diabetic subjects demonstrated no statistically significant difference between the fasting or postprandial blood glucose levels, although the diabetic group had larger differences in absolute serum glucose values.

- Candan *et al.* [21] prospectively studied a group of ten patients with DM2 and 29 patients without diabetes, who were treated with 80 mg of triamcinolone epidural injections. Fasting blood glucose levels increased significantly on the first two days after the injection (day 1, 125± 55.52 mg/dl with p= 0.002; day 2, 113.41± 35.19 mg/dl with p= 0.01) in all subjects. In nondiabetic subjects, fasting blood glucose values showed an increase of 12.70 % (109.24 [+ or -] 19.64 mg/dl) on the first day (p=0.001) compared to diabetic subjects who demonstrated an increase of 23.49 % (165.1 [+ or -] 69.11 mg/dl) on the first day (p=0.037). Fasting glucose levels returned to baseline values on the third day after injection in non-diabetic patients and returned to normal on the fourth day after injection in diabetic patients.

Studies have also shown that corticosteroid dose can affect the degree and duration of increased blood glucose. Mahmood *et al.* [22] prospectively compared the effect of epidural methylprednisolone 40 mg to 80 mg and methylprednisolone 40 mg on fasting and postprandial blood glucose levels in a group of 110 patients. The group that received 80 mg of methylprednisolone had significantly greater increases in blood glucose throughout the three-day follow-up period. Kim *et al.* [23] retrospectively compared the effect of epidural triamcinolone 20 mg to 40 mg in 100 diabetes patients. The group that received the higher dose of triamcinolone also had significantly greater glucose levels for three days. It is important to note that the higher the dose of injected corticosteroid, the greater the risk of postprocedural hyperglycemia and, therefore, the lowest effective dose of corticosteroid should be considered for injections in DM2 patients to avoid or shorten the duration of postprocedural hyperglycemia.

Overall, studies demonstrate that epidural corticosteroid injections with doses ranging from triamcinolone 20 mg (methylprednisolone 20 mg equivalent) to betamethasone 18 mg (methylprednisolone 120 mg equivalent) can cause elevations in both fasting and postprandial blood glucose levels during the first two days after an epidural injection, with elevated postprandial glucose seen up to four days after the procedure. No complications related to acute hyperglycemia were noted in any of these studies [19-23].

Conclusions

- Transient elevations in blood glucose levels are likely to occur after corticosteroid injections in patients with DM2.
- Despite this, there is a relatively low risk of significant hyperglycemia-related adverse effects, including a low risk of severe complications such as DKA and HHS. Accordingly, corticosteroid injections can typically be performed safely in patients with DM2, even if poorly controlled.
- Hyperglycemia after exposure to exogenous corticosteroids is likely dose-dependent, and as such, the lowest effective dose should be used.
- Patients with DM2 should be counseled regarding the risks of hyperglycemia and associated complications following corticosteroid injections, especially DKA and HHS.
- Patients should be counseled to monitor blood glucose levels frequently after corticosteroid injections for 72 hours post-injection, or until levels have returned to baseline.
- Patients should be educated on symptoms to be aware of that may be indicative of hyperglycemia.
- Patients should be aware of the appropriate steps to take if clinically significant hyperglycemia occurs, which may include adjusting medications under the advisement of the provider managing their DM2.
- If there is concern for DKA or HHS, the patient should be directed to the emergency department.
- Corticosteroid injections for musculoskeletal pain are elective, and if there is significant concern about hyperglycemia-related complications that may occur, the planned procedure can be canceled.

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