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Differential effects of oral versus intravenous hydrocortisone and dexamethasone on capillary blood glucose levels in adult inpatients – a single centre study

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ABSTRACT

Background: Corticosteroids raise blood glucose concentrations; however, it remains unknown which form of administration, oral or intravenous, is associated with the greatest degree of blood glucose rise in hospitalised patients. Furthermore, it is not known whether the pattern of the associated hyperglycaemia throughout the day differs depending on the route of administration.

Methods: This was a single centre retrospective study of 384 adult inpatients receiving oral or intravenous hydrocortisone and dexamethasone. Data on capillary glucose concentrations and time taken over 7 days were collected. A mixed model for repeated measures was applied to compare changes in glucose concentration over time for oral and intravenous corticosteroids. An auto-regressive covariance structure was employed to model correlations between repeated measurements. This was adjusted for age, sex, pre-admission diabetes, and/or pre-admission corticosteroid status.

Results: No significant difference was found between oral and intravenous hydrocortisone on day 1 or across all 7 days (mean difference 0.17 mmol/L (−1.39, 1.75), $p = 0.827$, and mean difference 0.20 mmol/L (−0.61, 1.01), $p = 0.639$ respectively). There were no differences in mean glucose concentrations between those on oral or intravenous dexamethasone on day 1 or across all 7 days (mean difference 0.41 mmol/L (−0.55, 1.38), $p = 0.404$ and mean difference −0.09 mmol/L (−1.05,0.87), $p = 0.855$, respectively).

Conclusion: This study found that oral and intravenous administration of hydrocortisone and dexamethasone do not have a significantly differing impact on blood glucose levels. Capillary glucose monitoring is strongly recommended in all individuals who are on either oral or intravenous corticosteroids.

Introduction

Corticosteroids are a widely used medication, with uses ranging from replacement for adrenal insufficiency to supraphysiological doses used in a variety of specialties for their anti-inflammatory and immunosuppressive effects.[1] The indication of corticosteroids has further increased as the RECOVERY (Dexamethasone in Hospitalised Patients with COVID-19) trial recommended the use of corticosteroids in patients with COVID-19 requiring oxygen.[2] The prevalence has been reported to be around 0.7% of the general population at any time, and one study showed that over 12% of adult inpatients in secondary care may be on corticosteroids and another showed that 20% of adults may be prescribed short course of steroids during a 3-year period.[3-5]

The administration of corticosteroids for their undoubted therapeutic benefits needs to be balanced with their extensive side effects profile. This includes steroid-induced hyperglycaemia and steroid-induced diabetes.[6] Steroid-induced hyperglycaemia refers to hyperglycaemia in people with a pre-existing diagnosis of diabetes, and steroid-induced diabetes refers to hyperglycaemia in people without a known diagnosis of diabetes.[7] This is thought to occur due to increased production of glucose from the liver, reduced uptake of glucose from muscle and adipose, increased insulin resistance, and perhaps even reduced beta cell function.[8-10] Previous data from our group have shown that dexamethasone and methylprednisolone are more likely to produce a greater extent of glucose rise than prednisolone and hydrocortisone, perhaps due to their greater potency and half-life.[11] Hyperglycaemia, including

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Table 1
Baseline characteristics of the adult inpatients on oral and intravenous corticosteroids who had blood glucose monitoring on day one. Data are given as number (%) of patients unless otherwise specified.

	Oral hydrocortisone $n = 27$	Intravenous hydrocortisone $n = 87$	Oral dexamethasone $n = 188$	Intravenous dexamethasone $n = 82$
Age, mean (SD)	61.6 (16.8)	68.1 (18.8)	70.1 (13.7)	63.6 (18.1)
Male	12 (44.4)	47 (54.0)	103 (54.8)	45 (54.9)
Female	15 (55.6)	40 (46.0)	85 (45.2)	37 (45.1)
Previous diagnosis of diabetes	10 (37.0)	42 (48.3)	68 (36.2)	22 (26.8)
Steroids before admission	22 (81.5)	32 (36.8)	48 (25.5)	6 (7.3)

Table 2
Mean differences in blood glucose concentrations of oral and intravenous (IV) hydrocortisone with 95% confidence interval on day 1 and all 7 days.

	Oral mean (mmol/L)	IV mean (mmol/L)	Mean difference	95% CI	*p* value
Day 1	8.92	8.75	0.17	(−1.39, 1.75)	0.827
Across 7 days	8.40	8.20	0.20	(−0.61, 1.01)	0.639

that from corticosteroids, can cause complications of increased hospital attendance, prolonged hospital stay, increased morbidity and increased mortality.[6,12] In the UK, the Joint British Diabetes Societies for Inpatient Care (JBDS) have created national guidelines that recommend monitoring of capillary blood glucose for all adults on oral or intravenous corticosteroids.[7]

It is known that administration of intravenous corticosteroids results in a quicker rise in blood glucose concentration than administration of oral corticosteroids, which produce a rise over 4–8 h.[7] However, the current evidence base does not demonstrate whether there is a difference in the extent of hyperglycaemia that intravenous corticosteroids may produce compared with oral corticosteroids. This is important to know to ensure that monitoring for hyperglycaemia is comprehensive and/or to suggest whether alternative corticosteroid administrations should be prescribed. Furthermore, these data could be used to inform guidelines, which currently do not differentiate recommendations between oral and intravenous corticosteroids.

A retrospective study was conducted on adult inpatients on oral or intravenous corticosteroids to investigate the following: is there a differential effect of oral versus intravenous corticosteroids on capillary glucose concentrations in adult inpatients? And is there a difference in the pattern of hyperglycaemia at each point of the day with each route of administration of the corticosteroid?

Materials and methods

This was a single centre retrospective study that was conducted at Norfolk and Norwich University Hospitals NHS Foundation Trust (Norwich, UK). Using an electronic medicine-prescribing and -administration system, all adult inpatients receiving oral or intravenous hydrocortisone and dexamethasone were identified between 10 February 2021 and 10 September 2021. Of the people identified, those with capillary glucose monitoring were included in this study. Individuals under 18 years of age, outpatients, those in the emergency department or with no capillary glucose monitoring, and people with corticosteroid administration by routes other than oral or intravenous were excluded. Data collected included: age and sex; pre-existing diabetes status; pre-admission corticosteroid use status; type, total daily dose, and route of administration of corticosteroid; capillary blood glucose concentrations; and times of glucose measurements. These data were collected from the first corticosteroid administration up to 7 consecutive days. This study was registered with the Clinical Audit and Improvement Department at the Norfolk and Norwich University Hospitals NHS Foundation Trust (registration DIAB_TW_23–24_P04). This study was considered a service-improvement exercise; therefore, no ethics approval was required.

Statistical analysis

The effects of oral and intravenous hydrocortisone and dexamethasone were compared using data from day 1 and across all 7 days. The mean of the capillary glucose concentrations measured during 4-h segments was calculated, resulting in up to six glucose measurements, and, over the 7 days, up to 42 glucose measurements. To compare changes in glucose concentration over time for oral and intravenous corticosteroids, a mixed model for repeated measures was applied. An auto-regressive covariance structure was employed to model correlations between repeated measurements. The repeated-measures model was adjusted for age, sex, pre-admission diabetes and/or pre-admission corticosteroids status. Data from days where no capillary blood glucose monitoring took place were excluded from the analysis.

Results

During the data collection period, 384 patients met the criteria to be included in the study. The number of blood glucose readings on day 1 ranged from one to 24. On day 1, 30% of patients ($n = 114$) were receiving hydrocortisone, of whom 23.7% ($n = 27$) were being given oral hydrocortisone and 76.3% ($n = 87$) were given it intravenously (IV). The remaining 70% ($n = 270$) received dexamethasone, of whom 69.7% ($n = 188$) were given it orally and 30.3% ($n = 82$) were given it IV. Of the patients who had hydrocortisone administered on day 1, 14% ($n = 16$) had a course that lasted 7 days, 75% ($n = 12$) of whom were on oral administration and 25% ($n = 4$) of whom were on IV administration. Of the patients who had dexamethasone administered on day 1, 29.3% ($n = 79$) had a course that lasted 7 days, 84.8% ($n = 67$) of whom were on oral dexamethasone and 15.2% ($n = 12$) of whom were on IV dexamethasone. The median (interquartile range, IQR) total daily doses of the corticosteroids administered over the course of the 7 days were: oral hydrocortisone, 32.1 mg (25.0–40.7 mg); intravenous hydrocortisone 150.0 mg (92.9–171.4 mg); oral dexamethasone, 6.0 mg (6.0–12.0 mg); and intravenous dexamethasone, 6.9 mg (6.0–8.0 mg). Table 1 shows summary of baseline characteristics.

Oral versus intravenous hydrocortisone

Table 2 shows that the adjusted mean capillary glucose concentrations on day 1 and across all 7 days between those administered oral hydrocortisone compared to intravenous hydrocortisone did not show a statistically significant difference. Patients with a previous diagnosis of diabetes had a greater mean blood glucose on day 1 and across all 7 days ($p \leq 0.001$). There was no difference in mean blood glucose levels for patients who were on corticosteroids before admission, compared with those who were not.

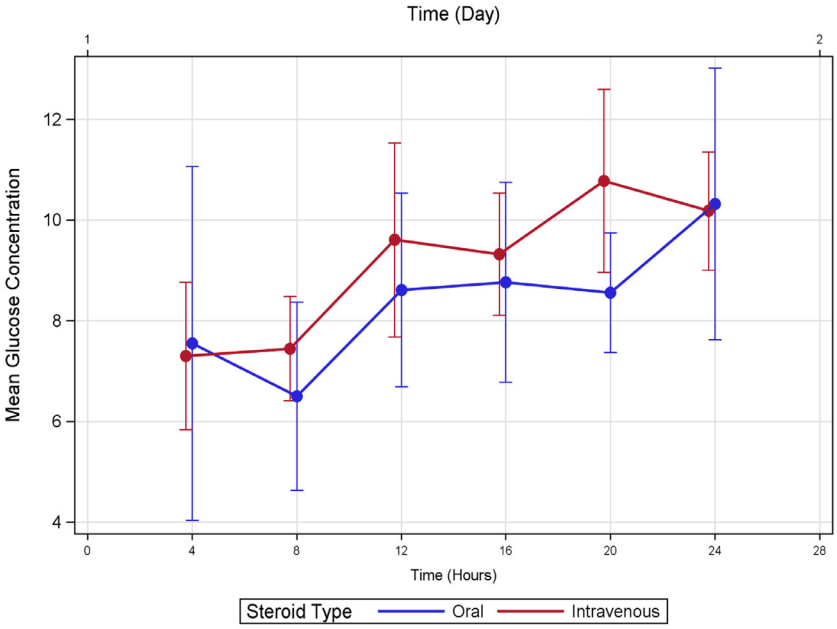

Fig. 1. Mean (95% CI) blood glucose concentrations (in mmol/L), as measured every 4 h on day 1 of treatment with oral and intravenous hydrocortisone.

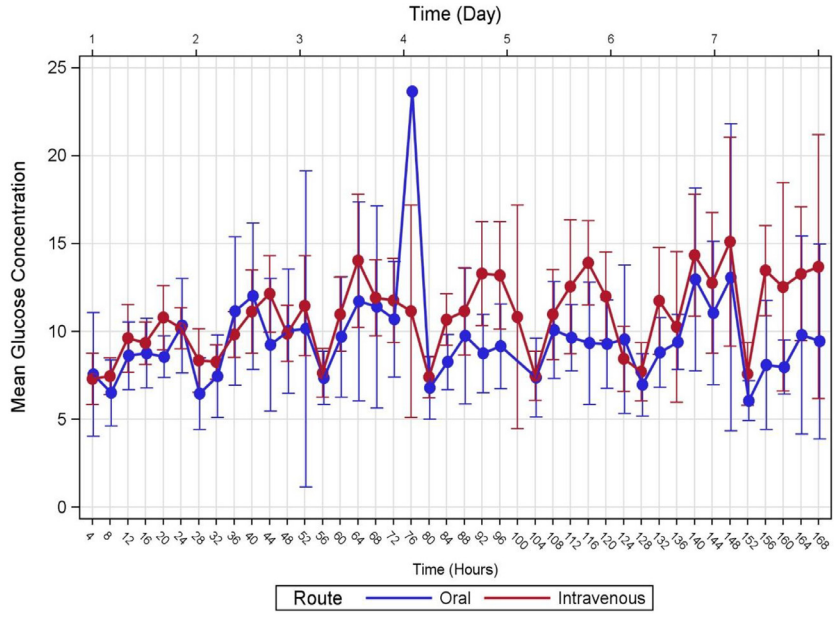

Fig. 2. Mean (95% CI) blood glucose concentrations (in mmol/L), as measured every 4 h across 7 days of treatment with oral and intravenous hydrocortisone.

Fig. 1 shows that on day 1, blood glucose concentrations between oral and intravenous hydrocortisone were not statistically significant different.

Fig. 2 shows that over 7 days, although not significant, average glucose levels in those given intravenous hydrocortisone were consistently higher, with a greater difference seen after 88 h.

Oral vs intravenous dexamethasone

On comparing adjusted average capillary blood glucose between patients being administered oral dexamethasone compared with intravenous dexamethasone, there was no significant difference on day 1 or across all 7 days, as seen in Table 3. Patients with a previous diagnosis of diabetes had a greater mean blood glucose on day 1 and across all 7 days ($p \leq 0.001$). Patients who were on corticosteroids before admission had a greater mean blood glucose across 7 days than those who were not (12.73 vs 10.35 mmol/L, $p \leq 0.001$).

Fig. 3 shows that on day 1, capillary glucose concentrations at each 4-h time point showed a statistically significant difference in the average blood glucose concentration at 20:00. Oral dexamethasone had a higher mean glucose concentration (11.6 mmol/L) than intravenous dexamethasone (8.9 mmol/L). This resulted in a mean difference of 2.7 mmol/L (95% CI: 0.7, 4.6; $p = 0.008$).

Fig. 4 shows that there was no statistically significant difference in glucose concentrations between oral and intravenous dexamethasone at any other 4-h time points on day 1 or across 7 days.

Discussion

Our study has shown that other than a transient difference seen towards the end of day 1 with oral dexamethasone use, no significant differences in mean glucose concentrations were seen when comparing oral vs intravenous hydrocortisone and dexamethasone. Patients administered dexamethasone who were also on corticosteroids prior to admis-

Table 3
Mean differences in blood glucose concentrations of oral and intravenous (IV) dexamethasone with 95% confidence interval on day one and all seven days.

	Oral mean (mmol/L)	IV mean (mmol/L)	Mean ifference	95% CI	*p* value
Day 1	9.55	9.14	0.41	(−0.55,1.38)	0.404
Across 7 days	11.50	11.59	−0.09	(−1.05,0.87)	0.855

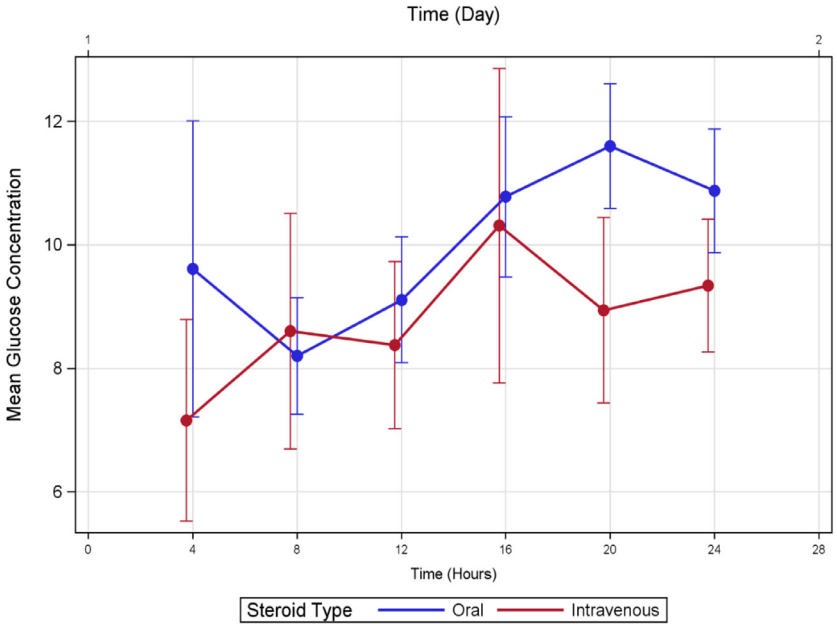

Fig. 3. Mean (95% CI) blood glucose concentrations (in mmol/L), as measured every 4 h on day 1 of treatment with oral and intravenous dexamethasone.

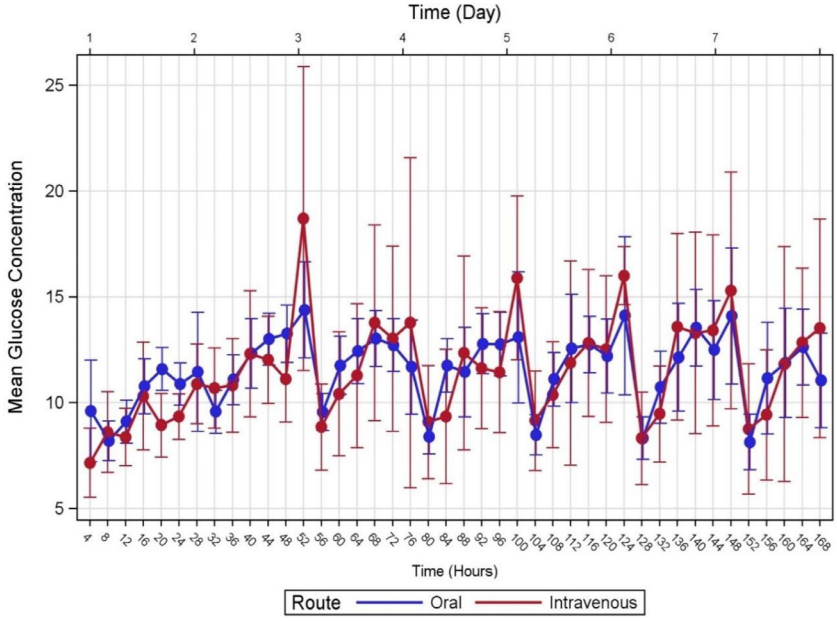

Fig. 4. Mean (95% CI) blood glucose concentrations (in mmol/L), as measured every 4 h across 7 days of treatment with oral and intravenous dexamethasone.

sion had a greater blood glucose over 7 days than those who were not on corticosteroids prior to admission.

Hyperglycaemia is known to have many harmful effects on people with and without diabetes. Generally, long-term use can cause macrovascular disease progression, increasing cardiovascular disease mortality.[13] Specifically, in hospitalised individuals with a new increase in blood glucose, it has been shown to increase the length of admission, increase the likelihood of transfer into intensive care units, impact direct discharge to home, and increase mortality.[14,15] This is a great concern because steroid-induced hyperglycaemia has been shown to be a common complication that occurs in hospitalised inpatients.[15,16] This has been seen to occur 1–2 days after initiation of the corticosteroid.[11,13]

It is known that oral corticosteroids have a lower potency than intravenous steroids; therefore, a higher dose is required to achieve the same effect.[17] More potent corticosteroids have been shown to cause a greater degree of glucose rise compared to oral corticosteroids.[11]

Currently, guidelines and recommendations for glucose monitoring do not differentiate between oral and intravenous corticosteroids.[7] This

study's findings, together with previous work,[11] could be considered in those with risk factors for steroid-induced hyperglycaemia. For those at risk, this study agrees with current guidelines to ensure vigorous monitoring for patients on both oral and intravenous steroids. This is recommended either pre- or post-lunch or evening meal.[7]

One of this study's main strengths is that it was a formed by a comprehensive retrospective data collection done over several months, looking at blood glucose levels over a 7-day period.

The limitations of the present study included that it is a single centre study with a predominantly white demographic. Given the retrospective nature of the data collection, we did not conduct a power calculation or calculate a sample size; thus, the study population size may not be large enough to detect a difference. The transient difference in blood glucose concentration with dexamethasone in day 1 may also be a false positive. The study did not differentiate between whether the hyperglycaemia was due to corticosteroids, a current illness, or poorly controlled diabetes. The study also only looked at the total daily corticosteroid dose, as opposed to differentiating between once-daily or multiple-daily dose regimens, which may impact mean blood glucose readings across time. Due to paucity in data, the findings do not consider the agents used for managing patients with hyperglycaemia, therefore it may be that, in some cases, the low increase in glucose concentrations was due to patients treated more aggressively with glucose-lowering agents.

Conclusion

This retrospective study found that no differences in mean glucose concentrations were seen when comparing oral vs intravenous hydrocortisone and dexamethasone. These findings could help raise awareness about the importance of regular monitoring of blood glucose in individuals who are on either oral or intravenous corticosteroids.

Consent for publication

This was a retrospective anonymous data collection exercise and patient consent was deemed by our audit department not to have been required.

Ethics approval and consent to participate

This study was registered with the Clinical Audit and Improvement Department at the Norfolk and Norwich University Hospitals NHS Foundation Trust (registration DIAB_TW_23-24_P04). This study was considered a service-improvement exercise; therefore, no ethics approval was required.

Data availability

Data will be available upon reasonable request.

CRediT authorship contribution statement

Vaishali Limbachia: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Ian Nunney:** Formal analysis. **Daniel J. Page:** Writing – original draft, Methodology, Data curation. **Hannah A. Barton:** Writing – original draft, Data curation. **Leena K. Patel:** Writing – original draft, Data curation. **Georgia N. Thomason:** Writing – original draft, Data curation. **Stephan L. Green:** Writing – original draft, Data curation. **Kieran F.J. Lewis:** Writing – original draft, Data curation. **Ketan Dhatariya:** Writing – review & editing, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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