Mortality and Specific Causes of Death in Endogenous Cushing's Syndrome: A Systematic Review, Meta-Analysis and Meta-Regression

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Background: Endogenous Cushing's syndrome (CS) refers to an inappropriate hypercortisolism usually caused by either Cushing's disease (CD) or adrenal CS (ACS). CS results in significant morbidity and excess mortality if untreated. Even in treated cases there is often a significant health burden. Due to the rarity of CS (incidence ~ 1/1M population) , single cohort studies have insufficient power for reporting accurate mortality data. Only one previous systematic review and meta-analysis for CS has been reported that limited its scope to the inclusion of specific CD subgroup. Aims: To perform a meta-analysis and meta-regression analysis of all-cause and specific cause -mortality amongst patients with benign endogenous CS.

Methods: The protocol was registered in PROSPERO (CRD42017067530). Searches were undertaken of PubMed, EMBASE, CINHAL, web of science and Cochrane Central from start until April 2019. The primary outcomes were proportion of mortality and SMR. The meta-analysis was done with STATA version 16.1 software. The I2 test, subgroup analysis and meta-regression statistics were used to assess heterogeneity among included studies.

Results: A total of 11,527 articles, were retrieved. 87 articles with 100 study cohorts containing 17,276 CS patients reporting mortality were included. Fifty-three study cohorts reported Cushing's disease (CD) patients, 27 study cohorts reported for adrenal CS patients and 20 studies cohorts reported on both types of CS. The overall SMR of all type CS was 2.91 (95% CI 2.41-3.68) with I2 =40.3%. The SMR for CD was 3.27 (95% CI 2.33-4.21) with I2 = 55.6%. The SMR in ACS was 1.62 (95% CI 0.08-3.16) with I2 =0.0%. The overall proportion of death in CS was 0.05 (95% CI 0.03-0.06) with I2 =51.86%; in CD was 0.04 (95% CI 0.03-0.06) with I2 = 62.7% and in ACS 0.06 (95% CI 0.04-0.11) with I2 = 40.3 %. The proportion of death during the 30-day operative period was highest before 1991 at 0.07 and decreased to 0.03 in 1991-2000 to 0.01 in 2001-2010 and zero after 2011. The causes of death reported across 64 studies were cardiac causes (24.7%), infection (14.4%), cerebrovascular diseases (9.4%), malignancy (9.0%), thromboembolism (4.2%), active disease (2.9%), and adrenal insufficiency (2.7%).

Conclusion: CS is associated with increase in overall mortality. Advances in operative techniques and care have decreased peri-operative mortality over a 20 year period. The causes of death highlight the need for aggressive management of cardiovascular risk, prevention of thrombo-embolism, infection control and a normalised cortisol level.

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