Progesterone for acute traumatic brain injury

Progesterone is a naturally produced hormone that has well-defined pharmacokinetics, is widely available, inexpensive, and has steroidal, neuroactive and neurosteroidal actions in the central nervous system. It is, therefore, a potential candidate for treating traumatic brain injury (TBI] patients. However, uncertainty exists regarding the efficacy of this treatment.

Systematic reviews

2016

Ma et al., updated the searches of the following databases: the Cochrane Injuries Group's Specialised Register (30 September 2016), the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 9, 2016), MEDLINE (Ovid; 1950 to 30 September 2016), Embase (Ovid; 1980 to 30 September 2016), Web of Science Core Collection: Conference Proceedings Citation Index-Science (CPCI-S; 1990 to 30 September 2016); and trials registries: Clinicaltrials.gov (30 September 2016) and the World Health Organization (WHO) International Clinical Trials Registry Platform (30 September 2016).

They included randomised controlled trials (RCTs) of progesterone versus no progesterone (or placebo) for the treatment of people with acute TBI.

Two review authors screened search results independently to identify potentially relevant studies for inclusion. Independently, two review authors selected trials that met the inclusion criteria from the results of the screened searches, with no disagreement.

They included five RCTs in the review, with a total of 2392 participants. We assessed one trial to be at low risk of bias; two at unclear risk of bias (in one multicentred trial the possibility of centre effects was unclear, whilst the other trial was stopped early), and two at high risk of bias, due to issues with blinding and selective reporting of outcome data.All included studies reported the effects of progesterone on mortality and disability. Low quality evidence revealed no evidence of a difference in overall mortality between the progesterone group and placebo group (RR 0.91, 95% CI 0.65 to 1.28, I^2 = 62%; 5 studies, 2392 participants, 2376 pooled for analysis). Using the GRADE criteria, we assessed the quality of the evidence as low, due to the substantial inconsistency across studies.There was also no evidence of a difference in disability (unfavourable outcomes as assessed by the Glasgow Outcome Score) between the progesterone group and placebo group (RR 0.98, 95% CI 0.89 to 1.06, I^2 = 37%; 4 studies; 2336 participants, 2260 pooled for analysis). We assessed the quality of this evidence to be moderate, due to inconsistency across studies.Data were not available for meta-analysis for the outcomes of mean intracranial pressure, blood pressure, body temperature or adverse events. However, data from three studies showed no difference in mean intracranial pressure between the groups. Data from another study showed no evidence of a difference in blood pressure or body temperature between the progesterone and placebo groups, although there was evidence that intravenous progesterone infusion increased the frequency of phlebitis (882 participants). There was no evidence of a difference in the rate of other adverse events between progesterone treatment and placebo in the other three studies that reported on adverse events.

This updated review did not find evidence that progesterone could reduce mortality or disability in patients with TBI. However, concerns regarding inconsistency (heterogeneity among participants and the intervention used) across included studies reduce our confidence in these results.There is no

evidence from the available data that progesterone therapy results in more adverse events than placebo, aside from evidence from a single study of an increase in phlebitis (in the case of intravascular progesterone).There were not enough data on the effects of progesterone therapy for our other outcomes of interest (intracranial pressure, blood pressure, body temperature) for us to be able to draw firm conclusions.Future trials would benefit from a more precise classification of TBI and attempts to optimise progesterone dosage and scheduling [1)].

2012

Ma et al., searched: the Cochrane Injuries Group's Specialised Register (13 July 2012), Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 7, 2012), MEDLINE (Ovid) (1950 to August week 1, 2012), EMBASE (Ovid) (1980 to week 32 2012), LILACS (12 August 2012), Zetoc (13 July 2012), Clinicaltrials.gov (12 August 2012), Controlled-trials.com (12 August 2012). SELECTION CRITERIA: We included published and unpublished randomised controlled trials (RCTs) of progesterone versus no progesterone (or placebo) for the treatment of people with acute TBI. DATA COLLECTION AND ANALYSIS: Two review authors independently screened search results to identify the full texts of potentially relevant studies for inclusion. From the results of the screened searches two review authors independently selected trials meeting the inclusion criteria, with no disagreement. MAIN RESULTS: Three studies were included with a total of 315 people. Two included studies were of high methodological quality, with low risk of bias in allocation concealment, blinding and incomplete outcome data. One study did not use blinding and had unclear risk of bias in allocation concealment and incomplete outcome data. All three studies reported the effects of progesterone on mortality. The pooled risk ratio (RR) for mortality at end of follow-up was 0.61, 95% confidence interval (CI) 0.40 to 0.93. Three studies measured disability and found the RR of death or severe disability in patients treated with progesterone to be 0.77, 95% CI 0.62 to 0.96. Data from two studies showed no difference in mean intracranial pressure or the rate of adverse and serious adverse events among people in either group. One study presented blood pressure and temperature data, and there were no differences between the people in the progesterone or control groups. There was no substantial evidence for the presence of heterogeneity.

Current clinical evidence from three small RCTs indicates progesterone may improve the neurologic outcome of patients suffering TBI. This evidence is still insufficient and further multicentre randomised controlled trials are required [2)].

2011

Junpeng et al., searched: the Cochrane Injuries Group's Specialised Register (to April 2010), Cochrane Central Register of Controlled Trials 2010, Issue 1 (The Cochrane Library), MEDLINE (Ovid) (1950 to April week 1 2010), EMBASE (Ovid) (1980 to week 14 2010), LILACS (to 17 April 2010), Zetoc (to 21 April 2010), Clinicaltrials.gov (17 April 2010), Controlled-trials.com (17 April 2010).

They included published and unpublished randomised controlled trials (RCTs) of progesterone versus no progesterone (or placebo) for the treatment of acute TBI.

Two authors independently screened search results to identify the full texts of potentially relevant studies for inclusion. From the results of the screened searches two authors independently selected trials meeting the inclusion criteria, with no disagreement.

Three studies were included with 315 patients. All three studies reported the effects of progesterone on mortality. The pooled relative risk (RR) for mortality at end of follow-up is 0.61, 95% confidence interval (CI) 0.40 to 0.93. Three studies measured disability and found the RR of death or severe disability in patients treated with progesterone was 0.77, 95% confidence interval (CI) 0.62 to 0.96. Two studies presented data on intracranial pressure and adverse events. One study presented blood pressure and temperature data. There was no substantial evidence for the presence of heterogeneity.

Current clinical evidence from three small RCTs indicates progesterone may improve the neurologic outcome of patients suffering TBI. This evidence is still insufficient and further multicentre randomised controlled trials are required [3)].

Progesterone has been associated with robust positive effects in animal models of traumatic brain injury (TBI) and with clinical benefits in two phase 2 randomized controlled trials. Skolnick et al, investigated the efficacy and safety of progesterone in a large, prospective, phase 3 randomized controlled trial.

A multinational placebo controlled study, in which 1195 patients, 16 to 70 years of age, with severe traumatic brain injury TBI (Glasgow Coma Scale score, ≤8 (on a scale of 3 to 15, with lower scores indicating a reduced level of consciousness and at least one reactive pupil) were randomly assigned to receive progesterone or placebo. Dosing began within 8 hours after injury and continued for 120 hours. The primary efficacy end point was the Glasgow Outcome Scale score at 6 months after the injury.

Proportional-odds analysis with covariate adjustment showed no treatment effect of progesterone as compared with placebo (odds ratio, 0.96; confidence interval, 0.77 to 1.18). The proportion of patients with a favorable outcome on the Glasgow Outcome Scale (good recovery or moderate disability) was 50.4% with progesterone, as compared with 50.5% with placebo. Mortality was similar in the two groups. No relevant safety differences were noted between progesterone and placebo.

Primary and secondary efficacy analyses showed no clinical benefit of progesterone in patients with severe TBI. These data stand in contrast to the robust preclinical data and results of early single-center trials that provided the impetus to initiate phase 3 trials. (Funded by BHR Pharma; SYNAPSE ClinicalTrials.gov number, NCT01143064 .) [4)].

There was no significant difference between the progesterone group and the placebo group in the proportion of patients with a favorable outcome (relative benefit of progesterone, 0.95; 95% confidence interval [CI], 0.85 to 1.06; P=0.35). Phlebitis or thrombophlebitis was more frequent in the progesterone group than in the placebo group (relative risk, 3.03; CI, 1.96 to 4.66). There were no significant differences in the other prespecified safety outcomes. Conclusions This clinical trial did not show a benefit of progesterone over placebo in the improvement of outcomes in patients with acute TBI. (Funded by the National Institute of Neurological Disorders and Stroke and others; PROTECT III ClinicalTrials.gov number, NCT00822900 .) [5)].

There is significant theoretical evidence for the potential role of estrogen and progesterone use in altering the pathogenesis of SAH. Nevertheless, this has received mixed reviews in both case controlled studies and cohort analysis within the literature [6)]

1)

Ma J, Huang S, Qin S, You C, Zeng Y. Progesterone for acute traumatic brain injury. Cochrane Database Syst Rev. 2016 Dec 22;12:CD008409. doi: 10.1002/14651858.CD008409.pub4. [Epub ahead of print] Review. PubMed PMID: 28005271.
2)

Ma J, Huang S, Qin S, You C. Progesterone for acute traumatic brain injury. Cochrane Database Syst Rev. 2012 Oct 17;10:CD008409. doi: 10.1002/14651858.CD008409.pub3. Review. PubMed PMID: 23076947.
3)

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Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, Nelson NR, Stocchetti N; the SYNAPSE Trial Investigators. A Clinical Trial of Progesterone for Severe Traumatic Brain Injury. N Engl J Med. 2014 Dec 10. [Epub ahead of print] PubMed PMID: 25493978.
5)

Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS, Barsan WG; the NETT Investigators. Very Early Administration of Progesterone for Acute Traumatic Brain Injury. N Engl J Med. 2014 Dec 10. [Epub ahead of print] PubMed PMID: 25493974.
6)

Young AM, Karri SK, Ogilvy CS. Exploring the use of estrogen & progesterone replacement therapy in subarachnoid hemorrhage. Curr Drug Saf. 2012 Jul;7(3):202-6. Review. PubMed PMID: 22950381.