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The inclusion of glutamine to oral rehydration therapy for the treatment of diarrhoea in pre-weaned calves.

Does inclusion of glutamine in oral rehydration solutions (ORS) improve recovery from mild-moderate diarrhoea in pre-weaned calves?

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Clinical scenario

Upon diagnosing mild-moderate diarrhoea in a pre-weaned calf you feel that your treatment strategy should comprise oral rehydration therapy. You have a choice of rehydration solutions available, some containing glutamine and some containing no glutamine. You want to treat the calf with a product that offers the best chance of recovery.

The question

In [pre-weaned calves with mild to moderate diarrhoea] does treatment with [ORS containing glutamine] compared with [ORS not containing glutamine] lead to [improved clinical recovery]?

Search parameters

(calf OR calv* OR bovi*) AND (ORT or ORS Or oral rehydrat*) AND (scour* OR diarr*) AND glutamine

Databases searched

- Medline: All years - 2015 Week 31, using Ovid SP interface
- CAB Abstracts: 1973 - 2015 Week 31, using Ovid SP interface

Limits: English language only

Search results

CAB Abstracts via Ovid SP: 8 papers found: 3 papers were considered irrelevant because they did not answer the question, 1 paper was inaccessible and 4 papers were considered relevant.

Medline via Web of Science: 6 papers found: 3 papers considered irrelevant because they did not answer the question, 2 relevant papers duplicated CAB Abstract results and one additional paper was considered relevant.

Total number of papers used: 5

Search last performed: 18th March 2016

SUMMARY OF EVIDENCE

Paper 1: The effect of oral rehydration in neonatal calves treated for diarrhoea induced with *Escherichia coli* (O101:K99) infection. (Pal and Pachauri 2008)

Patient group: Cross breed dairy bull calves experimentally infected with enterotoxigenic *E.coli* (O101:K99) (n=24). Group 1 received conventional ORS (n=6), group 2 received high calorie glutamine free ORS (n=6), group 3 received Ca-Mg nutrient ORS without glutamine and group 4 received Ca-Mg nutrient ORS with glutamine.

Study type: Non-blinded, non-randomised controlled trial.

Outcomes: Skin tenting, warmth of extremities, mucous membrane moistness, mucous membrane colour, faecal consistency and demeanour assessed twice daily for 4 days of treatment.

Key results: Ca-Mg nutrient oral rehydration solutions with glutamine appear to result in improvement in more clinical parameters (skin tenting ($p < 0.01$), mucous membrane colour ($P < 0.01$), mucous membrane moistness ($p < 0.05$), warmth of extremities ($p < 0.05$) and faecal consistency ($p < 0.05$)) than ORS without glutamine. Ca-Mg nutrient oral rehydration solutions with glutamine did not appear to improve the demeanour of the calves.

Study weaknesses: The exact breed of the calves is not stated. The method of allocation of calves to different groups is not explained. There is no power calculation reported and the study size is small ($n=24$). Assessors were not blinded to the treatment each group received. Although the authors report that the calves were 'similar' in weight and zinc-sulphate turbidity test result, it is not shown that any statistical tests were performed to show this. All of the parameters measured in the study are subjective and only one (faecal consistency) is given a quantitative score. Confidence intervals are not reported.

PAL, B. & PACHAURI, S. P. (2008) Effect of oral rehydration in neonatal calves treated for diarrhoea induced with *Escherichia coli* (O101:K99) infection. *Indian Journal of Veterinary Research* **17**:19-26

Paper 2: Detrimental effects on villus form during conventional oral rehydration therapy for diarrhoea in calves; alleviation by a nutrient oral rehydration solution containing glutamine (Brooks and others, 1998)

Patient group: Jersey bull calves $n=47$ experimentally infected with enterotoxigenic *E.coli*, assigned to one of five treatment groups; C= control group which were uninfected ($n=10$), D= Diarrhoeic calves sampled at the stage that treatment was initiated ($n=10$), W = treated with WHO-type ORS ($n=9$), N= treated with a nutrient (high glucose) ORS ($n=10$), G=treated with a nutrient (high glucose) ORS containing glutamine ($n=9$).

Study type: Non-blinded, non-randomised controlled trial

Outcomes: Blood gases, pH and packed cell volume measured by blood sampling. Villus surface area in proximal, mid and distal small intestine (PSI, MSI, DSI) was calculated following dissection, using standard morphometric techniques. Proximal and distal spiral colon samples (PC, DC) were examined for crypt depth and width; mitoses per crypt were counted in samples from all regions.

Key results: Non-diarrhoeic calves showed the expected gradient of villus length through PSI, MSI and DSI. PSI showed the greatest loss of villus length and surface area (50%) in non-treated calves with diarrhoea vs control group.

The loss of villus length was worse in calves treated with conventional ORS (W) compared with the two nutritional ORS: $W = 72.4 \pm 6.0\%$, $N \& G = 85.8 \pm 3.5\%$ ($p < 0.05$) as was surface area in the MSI and DSI. Villus length in MSI and DSI did not differ significantly between W and pre-treatment diarrhoea.

Only solution G was associated with a significantly lower mitotic activity than in the MSI and DS of diarrhoeic calves: $118.7 \pm 17.4\%$, $191.9 \pm 19.2\%$ ($p < 0.05$).

Diarrhoea increased crypt depth throughout the intestine (PSI, MSI, DSI, PC, DC). Such deepening was statistically significantly less in the colon of calves treated with the glutamine-ORS (G) than with W (104.1/-+3.1, 114.5+/-3.8; $p < 0.02$) or N, (119.9+/-4.7; $p < 0.02$).

Study weaknesses: No power calculation was reported, and the sample size was small ($n=47$). The study was not blinded and the method of allocation of calves to the different treatment groups is not explained. Non-treated diarrhoeic calves were sampled at the time that the other groups started treatment, these samples were taken 96h earlier in the disease process than from other groups. Due to the nature of the study design, only differences in recovery of the gut mucosa at 96h could be evaluated.

BROOKS, H. W., HALL, G. A., WAGSTAFF, A. J. & MICHELL, A. R. (1998) Detrimental effects on villus form during conventional oral rehydration therapy for diarrhoea in calves; alleviation by a nutrient oral rehydration solution containing glutamine. *Veterinary Journal* **155**:263-274

Paper 3: Evaluation of a glutamine-containing oral rehydration solution for the treatment of calf diarrhoea using an *Escherichia coli* model. (Brooks and others 1997)

Patient group: Dairy or dairy-cross calves experimentally infected with enterotoxigenic *E.coli* at 72 hours old ($n=46$)

Study type: Non-blinded, non-randomised controlled trial

Outcomes: Plasma volume, extracellular fluid volume, blood volume (approximated from plasma volume and PCV), blood biochemistry parameters (pH, bicarbonate, sodium, glucose), packed cell volume (PCV), bodyweight, Zinc Sulphate turbidity test.

Key results: A glutamine-containing, high-calorie rehydration solution was the only solution to improve plasma volume significantly within 48 h and sustain the improvement throughout treatment ($p < 0.02$). The glutamine-containing high-calorie solution was the only solution to correct packed-cell volume within 48 h and sustain the benefit to the end of treatment. Within the treatment period both glutamine-free high-calorie solutions produced a significant weight loss (N 2.3_+0.4 kg, $P < 0.001$; GF 2.6_+0.9, $P < 0.05$) whereas the glutamine- containing high-calorie solution (G) did not (0.5+ 0.4 kg).

Study weaknesses: No power calculation was reported, and the sample size was small ($n=47$). Calves were initially randomly allocated to treatment groups, but as the study progressed random allocation ceased. The study was not blinded. Confidence intervals are not reported. The beneficial effects of glutamine inclusion in the ORS can only be assumed for high-calorie ORT, not low-calorie glutamine-containing solutions. Confidence intervals are not reported.

BROOKS, H. W., WHITE, D. G., WAGSTAFF, A. J. & MICHELL, A. R. (1997) Evaluation of a glutamine-containing oral rehydration solution for the treatment of calf diarrhoea using an *Escherichia coli* model. *Veterinary Journal* **153**:163-170

Paper 4: Fallibility of plasma urea and creatinine as indices of renal function in diarrhoeic calves treated with conventional or nutritional oral rehydration solutions. (Brooks and others 1997)

Patient group: Pre-weaned jersey and jersey-cross calves at least 14 days of age, weighing approximately 25kg and were allowed to 'naturally develop' diarrhoea by being housed in pens that previously held diarrhoeic calves. . (n=13)

Study type: Non-blinded, non-randomised controlled trial

Outcomes: Bodyweight, extracellular fluid (ECF) volume, glomerular filtration rate (GFR), plasma urea, plasma creatinine, plasma glucose.

Key results: Feeding a nutrient ORS with glutamine resulted in a significant increase in glomerular filtration rate when compared to conventional ORS ($p < 0.01$).

Study weaknesses: No power calculation was reported, and the sample size was small. One calf from each treatment group had to be excluded from the analysis due to outlying results, thus further reducing the already small sample sizes. The study was not blinded and allocation of calves to the different treatment groups is not randomised. The calves were allowed to develop diarrhoea 'naturally' and so the pathogens causing diarrhoea in different calves may have varied. The two ORS differed not only in the inclusion of glutamine but also in the concentration of sodium and therefore any differences seen in the two treatment groups could also be attributable to the higher sodium content of the glutamine-containing solution.

BROOKS, H.W., GLEADHILL, A., WAGSTAFF, A.J. & MICHELL, A.R. (1997) Fallibility of plasma urea and creatinine as indices of renal function in diarrhoeic calves treated with conventional or nutritional oral rehydration solutions. *Veterinary Journal* **154**: 35-39

Paper 5: Intestinal metabolism of glutamine and potential use of glutamine as a therapeutic agent in diarrheic calves. (Nappert and others 1997)

Patient group: The review is focused on diarrhoea in calves, but includes studies of other species or generic biochemical and anatomical studies where no direct bovine studies are available.

Study type: Narrative literature review

Outcomes: The following areas were reviewed; structure and principal metabolic pathways, intestinal glutamine uptake, intestinal glutamine use in healthy animals, intestinal glutamine use in the catabolic state, glutamine supplementation and therapeutic considerations and glutamine use in calves with diarrhoea.

Conclusions: Endogenous glutamine may not be sufficient to meet metabolic needs during critical illness. Glutamine supplementation could provide a new approach to promote intestinal healing when treating animals with enteritis.

Study weaknesses: This narrative review was peer-reviewed, but not carried out with a systematic approach. The search parameters were not stated, and papers referenced were not subjected to critical appraisal. The review was conducted almost 20 years ago and new literature is likely to be available on the subject. Many of the findings are extrapolated from human studies, or are veterinary studies carried out in species other than cattle.

NAPPERT, G., ZELLO, G.A. & NAYLOR, J.M. (1997) Intestinal metabolism of glutamine and potential use of glutamine as a therapeutic agent in diarrheic calves. *Journal of the American Veterinary Medical Association* **211**: 547-53

Comments

The studies varied in quality and strength of evidence, with generally small sample sizes and the majority were published almost 20 years ago. Many different outcomes were measured between the studies including villus structure, plasma volume, packed-cell volume, renal parameters, demeanour and faecal consistency. One study was a narrative literature review which was peer-reviewed but not performed in a systematic way. All of the studies found inclusion of glutamine to a high calorie ORS was beneficial, however where inclusion of glutamine to a non-nutritious ORS was studied it did not have the same effect.

Bottom line:

The inclusion of glutamine to a high calorie ORS results in improved clinical recovery from diarrhoea in pre-weaned calves.