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OPEN PEER REVIEW

Is Elastography Useful in Assessing Necrotizing Enterocolitis in Rats?

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 7 Jun 2020 – 7 Jul 2020

Referee 1 Reviewer

MINOR REVISION 7 Jun 2020

Hi
Overall, this manuscript is methodologically appropriate, but the following points must be addressed:
1. The title is not very suitable for the purpose of the study.
2. Table 1:
2.1. These columns (median, min, max, rank, and z) must be deleted.
2.2. The total rows must be deleted.
3. Table 2 and 3: It is better to use the Friedman test rather than the Wilcoxon test to assess changes over time, and then use pairwise comparisons to determine significance; however, the significance level must be adjusted using the Bonferroni, Scheffe, or LSD method rather than set at 0.05 for each comparison. This issue must also be added to the statistical analysis section of the methods.

Referee 2 Reviewer

MINOR REVISION 29 Jun 2020

The manuscript is prepared in proper English with correct methods and references. The result of the study, which was conducted in rats, was promising for further studies in human neonates.

The fact that the study was conducted in a small number of rats should again be addressed in the conclusion, and the results cannot be generalized to human neonates confidently at this point.

In the method section, it is mentioned that autopsies were performed on all rats. It would be better to mention in the result section whether there was complete concordance between the biopsy and elastography findings.

It is mentioned that the elastography values at the 96th hour were significantly greater than those at the 0th, 24th and 48th hours in the control group. Is there an explanation for this finding? Were the biopsy results normal in all rats in the control group?

Editor-in-Chief

MAJOR REVISION 7 Jul 2020

Dear authors,
Your article needs Major Revision.
Regards

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Is Elastography Useful in Assessing Necrotizing Enterocolitis?

Referee Feedback Responses

Dear Referees,

We would like to thank you very much for your insightful and helpful feedback and believe these have led to significant improvements in this paper. We have done a major revision of the paper and incorporated your suggestions, all of which we agreed with. We have provided responses to each point and highlighted the changes that resulted in the paper accordingly.

In this document we have addressed every comment made by the referees. In our responses below we used the following conventions:

- Black font designates verbatim referee comments
- Blue font designates our responses to a comment
- Red font designates the corresponding changes that were placed inside the revised version of the paper. The red sections are for the referees' convenience so they may see what changed without having to search for it in the paper.

Again, thank you for your helpful comments and for the time taken in reviewing this paper.

Reviewer(s)' Comments to Author:
Reviewers' Comments:

Reviewer 1:
Hi
Totally, this manuscript according to methodologically is appropriate but the following points must be edited:
1. The title is not very suitable for study purpose
The title is revised as suggested.

Is Elastography Useful in Assessing Necrotizing Enterocolitis?

2. Table 1:
2.1. These columns (median, min, max, rank, and z) must be deleted.
2.2. The total rows must be deleted.

Table 1 is revised as suggested.

	Mann-Whitney U Test			
	n	**SD***	**Rank**	**p****

Terminal ileum (0. hour)	**Experimental group**	8	0.08	8.75	**0.878**
	Control group	8	0.08	8.25	
Terminal ileum (24. hour)	**Experimental group**	8	0.14	12.5	**0.001**
	Control group	8	0.10	4.5	
Terminal ileum	**Experimental group**	8	0.11	12.5	**0.001**
	Control group	8	0.09	4.5	
Terminal ileum (96. hour)	**Experimental group**	8	0.35	12.5	**0.001**
	Control group	8	0.11	4.5	

* SD: standard deviation
** p< 0.05
Table 1

3. Table 2 and 3: It is better, rather than Wilcoxon test, to be used of Friedman test for assessing change during time, and then, can be used of pairwise comparison for determining significance; but, the significance level must be considered by Bonferroni or Scheffe or LSD method not considered 0.05 in each comparison. Also, this issue must be added in statistical analysis section of method.

Friedman test was conducted, Tables 2 and 3 are revised, as suggested.

Table 2. The evaluation of terminal ileum values at various hours of ischemia in the study group (Friedman test).

	Friedman Test			
	N	**Mean**	**Standard Deviation**	**Standard Test Statistic**	**p**
Terminal ileum at 0h	8	0.86	0.08		

	24h				-1.649	0.121
	48h				-3.008	0.002*
	96h				-4.648	0.000*
Terminal ileum at 24h		8	1.36	0.14		
	48h				-1.549	0.121
	96h				-3.098	0.002*
Terminal ileum at 48h		8	1.92	0.11		
	96h				-1.549	0.121

Table 3. The evaluation of values at various hours of ischemia in the control group (Friedman test)

	Friedman Test				
	N	**Mean**	**Standard Deviation**	**Standard Test Statistic**	**p**
Terminal ileum at 0h	8	0.85	0.08		
24h				-0.968	0.333
48h				-2.324	0.121
96h				-3.679	0.000*

Terminal ileum at 24h		8	0.86	0.10		
	48h				-1.356	0.175
	96h				-2.711	0.004*
Terminal ileum at 48h		8	0.87	0.09		
	96h				-1.356	0.175

Reviewer 2:
Dear Authors
I reviewed your manuscript as" Can we use a new radiologic approach in Necrotizing Enterocolitis?"
The most important issue is whether we can apply this technique in alive human neonates or not, regarding this fact that neonates moves and are not still, also in neonates with NEC, significant ileus may cause great restriction in performing ultrasound because of air preventing crossing of ultrasound waves.
In conclusion you mentioned that this is a good method for evaluation of NEC in neonates but it is not evaluated in your study, as you just evaluated Dead rats not even alive ones which should be corrected.
There are also many writing and grammatical mistakes to be revised.
THE USE images are not provided.

The following paragraphs are added to the Discussion section in order to clarify the paper as suggested.

As it is known, we, as pediatric surgeons and clinicians, distinguish NEC by its clinical status. As only the causes of colitis are known, not only NEC, but also infective enteritis, Hirshprung Disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis and sepsis. While considering all these in differential diagnosis, clinical findings constitute the most important condition for us. Of course, assisted diagnostic methods are very precious but first of all, whether the patient has gastric retantion with milk intolarance, apne, letargy, heat instability and hipotansion. In addition to these physical examination findings, we look at complete blood count, CRP, sedimentation, abdominal ultrasonography, color doppler ultrasonography as an auxiliary test in diagnosis.

In this study, we created an experimental NEC model in newborn rats, we have observed at 24th, 48th, and 96th hour in live rats and elastographic data. Moreover,

there has been complete concordance between the biopsy and elastography findings.

Our aim in this experimental study is to pave the way for new research studies and reformalize elastography research in NEC diagnosis in clinical newborn babies.The result of the study which was done on rats was promising for conducting further studies on the human neonates.

We investigate the diagnostic performance of elastography, which is a new method for its use in this field in NEC that we experimentally created. The place of elastography requires different new studies as a future work.

Reviewer 3:
The manuscript is prepared in proper English with correct method and reference. The result of the study which was done on rats was promising for conducting further studies on the human neonates.

The fact that the study has been done in rats and in small number, should again be addressed in the conclusion and the generalization of the results to human neonates can not be done confidently at this point.

The following part is added to the Discussion section, as suggested.

Our study has been done in rats and in small number; therefore, the generalization of the results to human neonates can not be done confidently at this point.

In the method section, it has been mentioned that autopsy has been done in all rats, it is better be mentioned in the result section, whether there has been complete concordance between the biopsy and elastography findings.

The following part is added to the Result section, as suggested.

Moreover, there has been complete concordance between the biopsy and elastography findings.

It is mentioned that the elastography values in 96th hour were seen to be significantly greater than those at the 0th, 24th and 48th hours in the control group. Is there an explanation for this finding? Was the biopsy result normal in all control group?

The following part is added to the Result section, as suggested.

The reason for elastography values in 96th hour were seen to be significantly greater than those at the 0th, 24th and 48th hours in the control group depends on stress induction. The reason for this is a stress not to deliver the milk to newborn rat from the mother rats for 4 days which causes inflammal inflammation.

Reviewer 4:
Dear author,
The study is well designed and written.

I made comments about the discussion which needs revision.
Good luck

The following paragraphs are added to the Discussion as suggested.

...Our study has been done in rats and in small number; therefore, the generalization of the results to human neonates can not be done confidently at this point.

As it is known, we, as pediatric surgeons and clinicians, distinguish NEC by its clinical status. As only the causes of colitis are known, not only NEC, but also infective enteritis, Hirshprung Disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis and sepsis. While considering all these in differential diagnosis, clinical findings constitute the most important condition for us. Of course, assisted diagnostic methods are very precious but first of all, whether the patient has gastric retantion with milk intolarance, apne, letargy, heat instability and hipotansion. In addition to these physical examination findings, we look at complete blood count, CRP, sedimentation, abdominal ultrasonography, color doppler ultrasonography as an auxiliary test in diagnosis.

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We investigate the diagnostic performance of elastography, which is a new method for its use in this field in NEC that we experimentally created. The place of elastography requires different new studies as a future work.

Associate Editor's Comments:

Associate Editor 1:
The manuscript so called "can we use new radiological approach in diagnosis NEC" needs major revision by dear authors according to the comments of dear reviewers .Please respond to all questions and revised manuscript according them. There are some problems in the manuscript and may need more clarification such as at surgical method :"abdominal ileus was inserted through a median incision" what is the meaning of ileus ?Please describe better technique

The following section is revised in Materials and Methods section as suggested

The surgical procedure
All rats were sacrificed by the end of the 4th day under ether anesthesia. In order to see inflammation in tissues macroscopically, first, the skin was cleaned with a povidone-iodine solution. Then the abdomen was entered through a median incision

and a 2 cm terminal ileum segment was taken as a sample at a distance of about 1 cm to the ileocecal valve.

The following paragraphs are added to the Discussion as suggested.

...Our study has been done in rats and in small number; therefore, the generalization of the results to human neonates can not be done confidently at this point.

As it is known, we, as pediatric surgeons and clinicians, distinguish NEC by its clinical status. As only the causes of colitis are known, not only NEC, but also infective enteritis, Hirshprung Disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis and sepsis. While considering all these in differential diagnosis, clinical findings constitute the most important condition for us. Of course, assisted diagnostic methods are very precious but first of all, whether the patient has gastric retantion with milk intolarance, apne, letargy, heat instability and hipotansion. In addition to these physical examination findings, we look at complete blood count, CRP, sedimentation, abdominal ultrasonography, color doppler ultrasonography as an auxiliary test in diagnosis.

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We investigate the diagnostic performance of elastography, which is a new method for its use in this field in NEC that we experimentally created. The place of elastography requires different new studies as a future work.

2 Revision 1

4 comments · 31 Jul 2020 – 4 Aug 2020

Referee 2 Reviewer — ACCEPT — 31 Jul 2020

All the comments have been properly addressed.

Referee 1 Reviewer — ACCEPT — 1 Aug 2020

Hi
At present, this manuscript is methodologically appropriate.

Associate Editor — MINOR REVISION — 3 Aug 2020

The manuscript could be nearly accepted except for an additional minor revision, as mentioned by the dear reviewer. Please, dear authors, check the whole article for other grammatical errors not mentioned and resubmit it.

Editor-in-Chief — MINOR REVISION — 4 Aug 2020

Dear authors,
Your article needs Minor Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Is Elastography Useful in Assessing Necrotizing Enterocolitis in Rats?

Referee Feedback Responses

Dear Referees,

We would like to thank you very much for your insightful and helpful feedback and believe these have led to significant improvements in this paper. We have done a minor revision of the paper and incorporated your suggestions, all of which we agreed with. We have provided responses to each point and highlighted the changes that resulted in the paper accordingly.

In this document we have addressed every comment made by the referees. In our responses below we used the following conventions:

- Black font designates verbatim referee comments
- Blue font designates our responses to a comment
- Red font designates the corresponding changes that were placed inside the revised version of the paper. The red sections are for the referees' convenience so they may see what changed without having to search for it in the paper.

Again, thank you for your helpful comments and for the time taken in reviewing this paper.

Reviewer(s)' Comments to Author:
Reviewers' Comments:

Reviewer 1:
Dear author,
The paper looks good after revision.
There are some typos in the result and discussion sections need to be corrected prior to publication.
Regards.

Thank you for your valuable comments.
The typos in the Result and Discussion sections are corrected as suggested.

Reviewer 2:
Hi
At present, this manuscript is appropriate according to methodologically.

Thank you for your valuable comments.

Reviewer 3:
Dear Authors

Thank you for major revision, I recommend to add {a study on Rats} in title of article.

Thank you for your valuable comments.

The title is revised as suggested.

Is Elastography Useful in Assessing Necrotizing Enterocolitis in Rats?

Also the writing and grammatical mistakes are still present, the article needs a thorough English revision and Its certificate must be uploaded. Some of the mistakes are as following: hypotansion(hypotension is correct), hematocheziadue? Inflammal? And some similar mistakes to be corrected.

The paper is reviewed by an English Language editing service as suggested.
The typos are corrected as suggested.

Reviewer 4:
All the comments have been properly addressed.

Thank you for your valuable comments.

Associate Editor's Comments:

Associate Editor 1:
The manuscript could be nearly accepted except for additional minor revision as mentioned by dear reviewer . Plz dear authors check whole article for depiction of some other non mentioned grammatical errors and resend it as soon as possible.

Thank you for your valuable comments.
The paper is reviewed by an English Language editing service as suggested.

3 Revision 2

2 comments · 21 Aug 2020 – 13 Dec 2020

Associate Editor

ACCEPT 21 Aug 2020

Regarding the second revision of the manuscript entitled " Is elastography useful in assessing NEC in rats?" and the appropriate changes made by the authors, as noted by the reviewers, it is now ready for publication in IJR.

Editor-in-Chief

MINOR REVISION 13 Dec 2020

Dear authors,
Your article needs Minor Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

CORRECTIONS:

1-In the materials and methods, is it Elaxto or Elasto? If so, please change it all through the manuscript.

"corrected as below"

The combination of gray-scale US and elastography was performed by a 4-13 MHz with an average of 12MHz bandwidth linear probe in Esaote Ultrasonography Systems, MyLab60 model, produced in Geneva, Italy; with ElaXto imaging application.

2- In the materials and methods, the sentence ends with a parenthesis. Where does this parenthesis start?

'corrected in manuscript"

3-In the introduction, you have mentioned, "Acute syllable are the main causes of morbidity." What does syllable mean. Please revise and correct.

'corrected as below"

Acute spontaneous intestinal perforation is the main cause of mortality.

4-In the introduction, "Although USE has a particularly diagnostic effect in the pathologies of parenchyma, Doppler USE is a more significant entity in demonstrating the absence of flow in blood vessel.[3-4]"
It seems that the first USE may be ultrasonography. Is it elastic ultrasonography or is it ultrasonography? Please revise and correct both USE in this sentence if necessary.

'corrected as below"

Although US has a particularly diagnostic effect in the pathologies of parenchyma, Doppler US is a more significant entity in demonstrating the absence of flow in blood vessel

5-In radiological assessment, "The combination of gray-scale US and elastography was performed with a 4-13 MHz MHz with an average of 12MHz bandwidth linear probe in Esaote Ultrasonography Systems, MyLab60 model, produced in Geneva, Italy; with Elaxto imaging application)."
The sentence ends with a closing parenthesis. Where is the opening parenthesis? Please revise and correct.

‘corrected as below”

The combination of gray-scale US and elastography was performed by a 4-13 MHz MHz with an average of 12MHz bandwidth linear probe in Esaote Ultrasonography Systems, MyLab60 model, produced in Geneva, Italy; with ElaXto imaging application.

6-In the statistical analysis, please add the manufacturer characteristics for SPSS.

‘corrected as below”

The study data were assessed with SPSS 20.0 package program (SPSS version 20.0 SPSS, IBM, NY, USA).

7-In the discussion, “In the visual examination of the operating segments, color change and stiffness coarse tissue stiffness of intestinal loops, and edema air cysts can be macroscopically observed.”
What does “stiffness coarse tissue stiffness of intestinal loops” mean? What does “edema air cysts” mean? Please revise and correct.

‘corrected as below”

In the visual examination of the operating segments, color change and tissue stiffness of intestinal loops, and edema can be macroscopically observed.

8-In the discussion, “As only the causes of colitis are known, not only NEC, but also infective enteritis, Hirshprung disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis and sepsis.”
This sentence is unclear. The sentence has no verb. Please revise and correct.

‘corrected as below”

The main causes of colitis are infective enteritis, Hirshprung Disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis, sepsis and NEC. Clinical findings such as gastric retention with milk intolerance, apnea, lethargy, heat instability and hypotension constitute important conditions, thus the assisted diagnostic methods are very precious in differential diagnosis.

9-In the discussion, “While considering all these in differential diagnosis, clinical findings constitute the most important condition.”
This sentence is not clear. Please revise and correct.

‘corrected as below”

The main causes of colitis are infective enteritis, Hirshprung Disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis, sepsis and NEC. Clinical findings such as gastric retention with milk intolerance, apnea, lethargy, heat instability and hypotension constitute important conditions, thus the assisted diagnostic methods are very precious in differential diagnosis.

10-In the discussion, “Of course, assisted diagnostic methods are very precious but first of all, whether the patient has gastric retention with milk intolerance, apnea, lethargy, heat instability and hypotension.
The second part of the sentence has no verb. Please revise and correct.

‘corrected as below”

The main causes of colitis are infective enteritis, Hirshprung Disease, ileal atresia, volvulus, meconium ileus, invagination, neonatal appendicitis, sepsis and NEC. Clinical findings such as gastric retention with milk intolerance, apnea, lethargy, heat instability and hypotension constitute important conditions, thus the assisted diagnostic methods are very precious in differential diagnosis.

11-In the discussion, “Our aim in this experimental study was to pave the way for new research studies and reformalize elastography research in NEC diagnosis in clinical newborn babies.’

What does “reformalize” mean? Please choose a more appropriate word.

‘corrected as below”

Our aim in this experimental study is to pave the way for new research studies and consider elastography research in NEC diagnosis in clinical newborn babies.

12-In tables 1 and 2, please add data for 96 hours.

‘corrected in the manuscript”

13-In table 2, what does standard test statistic mean? Please change to a correct statistic phrase.

“corrected in the manuscript”

4 Revision 3

1 comment · 3 Jan 2021

Editor-in-Chief

ACCEPT 3 Jan 2021

Dear authors,
Your article is acceptable for publication in IJR.
Regards