Comparison of Hand-sewn Direct Repair Versus Resection and Hand-sewn Anastomosis Techniques for the Reversal of Diverting Loop Ileostomy After Low Anterior Rectal Resection: A Randomized Clinical Trial

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Research Article

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Abstract

Background

This is the first randomized clinical trial evaluating and comparing bowel function and early and late outcomes of two different hand-sewn surgical techniques used for the closure of diverting protective loop ileostomy.

Methods

In this prospective, randomized, single-blind clinical trial, a total of 40 patients with a history of rectal cancer, low anterior resection, and diverting loop ileostomy who were candidates for ileostomy reversal were included. The patients were randomly assigned into two groups, including hand-sewn direct repair of the ileal defect (group A) and resection and hand-sewn anastomosis of the ileum (group B). One patient in group A lost the follow-up and excluded from the study.

Results

The mean age of patients was 56.42±10.47 and 52.10±10.24 years in groups A and B, respectively. Evaluating the early postoperative period, group A developed an earlier first gas passage (1.68±0.74 vs. 2.25±0.91 days, p<0.05) and stool passage (2.10±0.93 vs. 2.80±1.00 days, p<0.05). The oral diet was also tolerated significantly earlier in group A (p<0.05). Group A also revealed shorter operating time (83.68±8.95 vs. 89.50±8.09 minutes, p<0.05) and hospital stay (4.73±0.73 vs. 6.80±2.39 days, p <0.05). None of the participants in both groups developed signs of bowel obstruction during the early and late postoperative follow-up period.

Conclusions

Direct hand-sewn repair for the closure of diverting loop ileostomy is a safe technique with better postoperative bowel function, oral diet tolerance, and less hospital stay compared to resection and hand-sewn anastomosis of the ileum.

Trial registration:

This prospective RCT was carried out at the Tehran University of Medical Sciences, Tehran, Iran. This study was approved by the Research Ethics Committee of Tehran University of Medical Sciences (reference number: IR.TUMS.VCR.REC.1395.494). Trial registration: Iranian Registry of Clinical Trials (URL: http://en.irct.ir/trial/9335 ), registration number: IRCT201703158861N2, Registration date: 08/05/2017. The WHO International Clinical Trials Registry Platform (ICTRP), (URL: https://trialssearch.who.int/Trial2.aspx?TrialID=IRCT201703158861N2)
Creation of Loop ileostomy for fecal diversion is a common surgical procedure used to control possible complications of rectal anastomosis, especially anastomotic leakage in patients undergoing low anterior resection for distal rectal cancers. (1–5) Closure of the loop ileostomy usually performs 6 to 12 weeks after the primary surgery except in patients requiring adjuvant chemotherapy. (6) Although it is generally believed that ileostomy closure is an easy and safe procedure, the reported morbidity and mortality rates are 9.3%-67% and 1.7%-6.4%, respectively. (7–17) The most important complication after ileostomy closure is anastomotic leakage, which is reported after around 3% of procedures. This leakage prolongs hospitalization and increases the risk of permanent ostomy. (12)

Several techniques have been proposed for the closure of loop ileostomy. The most used technique is resection of the involved part of the ileum and anastomosis using hand-sewn or stapled anastomosis. Proponents of the stapled anastomosis believe that it makes an anastomosis which has a larger diameter compared to the hand-sewn anastomosis and reduces the risk of bowel obstruction. Conversely, hand-sewn anastomosis is more cost-effective. (18–21) Different methods of ileostomy closure have been compared with each other in terms of their outcome (such as days to the gas passage, defecate, and oral diet tolerance), complications (such as anastomotic leakage, stenosis, and wound infection), surgical time, and hospital stay. In most of the studies, there were no significant differences between the hand-sewn and the stapled anastomosis. (13, 22–24)

Simple repair of the ileal defect made during the creation of loop ileostomy is another technique used for the closure. In this procedure, which is named direct repair, the ostomy is separated from the abdominal wall, and the edges of the antimesenteric defect of the ileum are sutured together. The intact mesenteric ileal side and the mesentery of the ileum may lead to some functional advantages for this technique. In a review of the recent literature, we found no studies comparing the two hand-sewn techniques of direct repair and resection and anastomosis for the reversal of loop ileostomies. Therefore, it was decided to design a randomized clinical trial to compare functional outcomes and complications of these two techniques. This is the first clinical trial conducted on this topic, and it can open up an important domain helping surgeons choose the best hand-sewn technique for closure of loop ileostomies.

**Methods**

**Study design and setting**

This is a prospective, randomized, single-blind clinical trial which was performed at the colorectal surgery division of department of surgery at Tehran University of Medical Sciences between September 1, 2016 and December 1, 2018. This study has been approved by the Research Ethics Committee of Tehran University of Medical Sciences (27th August 2016) and registered on 08/05/2017 at the Iranian Registry of Clinical Trials (www.irct.ir) with the registration number of IRCT201703158861N2. A total of 40 patients were enrolled by MM to participate in this study. Patients with a history of rectal cancer who had undergone curative low anterior resection for rectal cancer and a diverting protective loop ileostomy were enrolled in this study (n= 40). Patients with a history of immunodeficiency, complications associated with
rectal anastomosis, including anastomotic leakage, para-anastomotic sinuses, and previous abdominal operation other than rectal cancer surgery, were excluded (n=0). All patients were randomly assigned into two groups using randomly permuted blocks method. Random allocation sequence was generated by the online platform www.randomization.com.

First group (Group A) included patients scheduled for the hand-sewn direct repair technique and second group (Group B) for hand-sewn resection and anastomosis of the ileum. All patients were informed of the study protocol, explained the surgical techniques, their benefits, and possible complications. Written informed consent was obtained from all participants. Allocation concealment was performed using random groups (A or B) in sealed envelopes which was opened in the operation room then that specific intervention was assigned to the participant by MK. MKa, MM and MA assessed the outcome and were blinded after assignment to interventions. This trial still continues and in the second phase three groups with three interventions will be evaluated and compared.

**Intervention And Surgical Techniques**

In both groups, the operation was done under general anesthesia and in the supine position. Skin preparation and sterile draping were done. The skin around the ileostomy (1 to 2 millimeters from the lateral edge of the ostomy) was opened to release the ileostomy from the abdominal wall; then, the subcutaneous tissue was opened to reach the fascial surface. The intestine was then completely mobilized from the surrounding tissues and the fascia to reach the intraperitoneal cavity. Attempts were made to minimize any iatrogenic trauma to the ileum.

In group A (hand-sewn direct repair group), the edges of the antimesenteric defect on the ileum - which had been created for the ileostomy - became fresh, then sutured using 3-0 Vicryl stitches in interrupted Gambee suture patterns. Interrupted seromuscular sutures of 3-0 silk were placed to reinforce the sutures. In group B (hand-sewn resection and anastomosis of the ileum), a small section (less than 1 centimeter) of the ileum proximal and distal to the site of ostomy was resected. The two ends of the ileum were sutured using 3-0 Vicryl stitches in interrupted Gambee suture patterns. Interrupted seromuscular sutures of 3-0 silk were placed to reinforce the sutures.

In both groups, after proper hemostasis, the fascial defect was repaired utilizing separate 0 Nylon stitches. The skin was restored using 2-0 Monocryl sutures in a purse-string fashion.

**Outcomes And Postoperative Follow-up**

After the operation, the patients were transferred to the surgical ward. During postoperative visits, if signs of ileus, including nausea, vomiting, and abdominal distention, were not found, the oral diet was initiated. The patients were asked to try a liquid diet; if tolerated, the diet was changed to the soft, and then to the regular diet. Information about the time of gas passage, defecation, and oral feeding (including tolerance
of liquid, soft and regular diet) after the operation was recorded. Potassium (K) and sodium (Na) were measured and recorded daily postoperatively. Serum potassium levels of less than 3.5 mEq/L and serum sodium levels of less than 135 mEq/L were considered as hypokalemia and hyponatremia, respectively.

After discharge, the patients were visited in the first week, first month, and then every three months up to at least six months in the colorectal surgery clinic. In follow-ups, patients were asked about possible symptoms of obstruction, including constipation, obstipation, abdominal distention, nausea, and vomiting. The physical examination was done in each visit.

Sample Size Calculation

Considering a study power of 80% and an α-level of 5%, a minimum sample size of 40 participants were calculated. The sample size was divided between the two groups of the study. Each group consisted of 20 participants.

Statistical analysis

SPSS software version 25 (IBM SPSS Statistics for Windows, IBM Corp, Chicago, IL) was utilized for statistical analysis. Student t-test was used to analyze quantitative data. P-values less than 0.05 were regarded as statistically significant. Categorical data will be shown as number and percent, and continuous data as mean and standard deviation.

Results

In this study, a total of 40 patients were randomly assigned to two equal groups of 20. Patients in group A underwent handsewn direct repair for the ileostomy reversal. From the 20 patients initially included in group A, 19 patients completed the follow-up after the procedure. One patient in the group A, lost the follow-up session and was excluded from the study. In group B, 20 patients underwent resection and handsewn anastomosis procedure for the ileostomy closure. All the patients recruited in group B completed their follow-up. (Figure 1)

Participants And Baseline Characteristics

Participants included 12 males and 7 females (male/female ratio:1.7) in group A and 13 males and 7 females (male/female ratio: 1.8) in group B (p >0.05). The mean (± standard deviation) age of patients was 56.42±10.47 and 52.10±10.24 years in groups A and B, respectively (p>0.05). The demographic data and clinical characteristics of the participants in both groups are presented and compared in Table 1. As shown in the table, both groups were statistically similar in terms of baseline and demographic variables. Preoperative laboratory studies, including hemoglobin level, white blood cell count and albumin level were also similar between the two groups (Table 1)
## Table 1
Demographic data and clinical characteristics of the participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type of Ileostomy Closure</th>
<th>Mean Difference [95% CI] **</th>
<th>p-value ***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand-sewn Direct Repair (N=19) *</td>
<td>Resection and Hand-Sewn Anastomosis (N=20) *</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.42 (±10.47)</td>
<td>52.10 (±10.24)</td>
<td>4.32 [-2.40 – 11.04]</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 12 (63.2%)</td>
<td>13 (65.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Female 7 (36.8%)</td>
<td>7 (35.0%)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>24.09 (±2.79)</td>
<td>22.84 (±3.71)</td>
<td>1.25 [-0.89 – 3.39]</td>
</tr>
<tr>
<td>Past Medical History</td>
<td>Hypertension 1 (5.3%)</td>
<td>2 (10.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Coronary Artery Disease 0 (0.0%)</td>
<td>2 (10.0%)</td>
<td>0.487</td>
</tr>
<tr>
<td></td>
<td>Diabetes Mellitus 0 (0.0%)</td>
<td>2 (10.0%)</td>
<td>0.487</td>
</tr>
<tr>
<td>Medication History</td>
<td>Antihypertensive 1 (5.3%)</td>
<td>1 (5.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Antiglycemic 0 (0.0%)</td>
<td>1 (5.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Antilipemic 0 (0.0%)</td>
<td>1 (5.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td>Other drugs 0 (0.0%)</td>
<td>2 (10.0%)</td>
<td>0.487</td>
</tr>
<tr>
<td>Habit History</td>
<td>Cigarette smoking 4 (21.1%)</td>
<td>7 (35.0%)</td>
<td>0.480</td>
</tr>
<tr>
<td></td>
<td>Opioid consumption 1 (5.3%)</td>
<td>1 (5.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Distance of the primary rectal tumor from the anal verge (cm)</td>
<td>8.10 (±1.85)</td>
<td>7.40 (±2.54)</td>
<td>0.70 [-0.74 – 2.14]</td>
</tr>
<tr>
<td>Preoperative Hemoglobin (g/dl)</td>
<td>12.13 (±1.21)</td>
<td>12.54 (±1.33)</td>
<td>-0.41 [-1.24 – 0.42]</td>
</tr>
</tbody>
</table>

* Categorical data are presented as number(percent), and continuous data as mean (±standard deviation).

** Mean difference with 95% Confidence Interval (CI) has been shown for continuous variables as well.

*** p-values < 0.05 were regarded as statistically significant.
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type of Ileostomy Closure</th>
<th>Mean Difference [95% CI] **</th>
<th>p-value ***</th>
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<tbody>
<tr>
<td></td>
<td>Group A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand-sewn Direct Repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=19) *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative white blood cell (WBC) count (×10^3/microliter)</td>
<td>4.95 (±1.17)</td>
<td>5.28 (±1.72)</td>
<td>-0.33 [-0.13 – 0.63]</td>
</tr>
<tr>
<td>Preoperative serum albumin (g/dl)</td>
<td>3.91 (±0.33)</td>
<td>4.09 (±0.39)</td>
<td>-0.17 [-0.41 – 0.06]</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection and Hand-Sewn Anastomosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=20) *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Categorical data are presented as number(percent), and continuous data as mean (±standard deviation).

** Mean difference with 95% Confidence Interval (CI) has been shown for continuous variables as well.

*** p-values < 0.05 were regarded as statistically significant.

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### Intraoperative Findings And Complications

According to the results of this study, accidental iatrogenic small bowel wall injury happened during the mobilization of stoma and enterolysis in 2 (10.5%) patients of group A and 3 (15%) patients of group B, which did not show any significant difference. However, the duration of the operation was significantly longer in group B (89.50±8.09 minutes) compared to group A (83.68±8.95 minutes) (p<0.05). Intraoperative blood loss was estimated at around 27±4.7 and 36±7.5 millimeters in groups A and B, respectively. This showed a significantly higher blood loss in group B (p<0.05). Intraoperative findings and complications are presented in Table 2.
### Table 2
Intraoperative findings and complications

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type of ileostomy closure</th>
<th>Mean Difference [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Group A</strong></td>
<td><strong>Group B</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand-sewn</td>
<td>Resection and Hand-Sewn</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Direct Repair</td>
<td>Anastomosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=19) *</td>
<td>(N=20) *</td>
<td></td>
</tr>
<tr>
<td>Duration of operation (minutes)</td>
<td>83.68 (±8.95)</td>
<td>89.50 (±8.09)</td>
<td>-5.81 [-11.34 – -0.28] 0.040 ***</td>
</tr>
<tr>
<td>Estimated intraoperative blood loss (millimeters)</td>
<td>27 (±4.7)</td>
<td>36 (±7.5)</td>
<td>-9.1 [-13.2 – -5.0] &lt;0.001 ***</td>
</tr>
<tr>
<td>Intraoperative accidental (iatrogenic) ileal damage</td>
<td>Thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial</td>
<td>2 (10.5%)</td>
<td>3 (15.0%)</td>
</tr>
<tr>
<td></td>
<td>Complete</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Location</td>
<td>Proximal ileal loop</td>
<td>2 (10.5%)</td>
<td>1 (5.0%)</td>
</tr>
<tr>
<td></td>
<td>Distal ileal loop</td>
<td>0 (0.0%)</td>
<td>1 (5.0%)</td>
</tr>
<tr>
<td></td>
<td>Proximal and distal ileal loops</td>
<td>0 (0.0%)</td>
<td>1 (5.0%)</td>
</tr>
</tbody>
</table>

* Categorical data are presented as number(percent), and continuous data as mean (±standard deviation).

** Mean difference with 95% Confidence Interval (CI) has been shown for continuous variables as well.

*** p-values < 0.05 were regarded as statistically significant.

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**Early Postoperative Follow-up**

Participants in group A tolerated oral liquid, soft and regular diet significantly faster than the other group (p<0.05). They also developed earlier first postoperative gas passage and defecation compared to group B (p<0.05). On average, patients in group A stayed in the hospital around 2 days shorter than group B (4.7 versus 6.8); it showed a significant difference. Data regarding hospital stay, diet tolerance, and bowel function are presented in Table 3.
Hypokalemia (K<3.5 mEq/L) was detected in 3 (15.8%) patients in group A and 3 patients (15%) of group B (p=1.000). Hyponatremia was only found in 4 (20%) patients of group B. Although none of the participants in Group A developed postoperative hyponatremia, this difference was not statistically significant (p=0.106). Anastomotic leakage and complete/partial bowel obstruction did not occur during the early postoperative period in any group of patients.

Table 3
Early postoperative follow-up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type of ileostomy closure</th>
<th>Mean difference [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand-sewn Direct Repair</td>
<td>Resection and Hand-Sewn Anastomosis</td>
<td></td>
</tr>
<tr>
<td>(N=19) *</td>
<td></td>
<td>(N=20) *</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>4.73 (±0.73)</td>
<td>6.80 (±2.39)</td>
<td>-2.06 [-3.22 – -0.90]</td>
</tr>
<tr>
<td>Bowel Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First gas passage (days)</td>
<td>1.68 (±0.74)</td>
<td>2.25 (±0.91)</td>
<td>-0.56 [-1.10 – -0.02]</td>
</tr>
<tr>
<td>First defecation (days)</td>
<td>2.10 (±0.93)</td>
<td>2.80 (±1.00)</td>
<td>-0.69 [-1.32 – -0.06]</td>
</tr>
<tr>
<td>Diet Tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid diet tolerance (Days)</td>
<td>1.84 (±0.68)</td>
<td>2.80 (±0.95)</td>
<td>-0.95 [-1.49 – -0.41]</td>
</tr>
<tr>
<td>Soft diet tolerance (days)</td>
<td>2.05 (±0.23)</td>
<td>3.40 (±0.26)</td>
<td>-1.34 [-2.06 – -0.62]</td>
</tr>
<tr>
<td>Regular diet tolerance (days)</td>
<td>3.21 (±0.23)</td>
<td>4.40 (±0.29)</td>
<td>-1.18 [-1.95 – -0.42]</td>
</tr>
</tbody>
</table>

* Data are presented as mean (±standard deviation).

** p-values < 0.05 were regarded as statistically significant.

Late Postoperative Follow-up

Patients were followed up for at least 6 months after the operation. Complications including re-hospitalization, entero-cutaneous fistula, anastomotic leakage, partial/complete bowel obstruction, and death did not occur in any groups of patients. This clinical trial still continues and in the second phase another intervention will be evaluated and compared to the existing two.

Discussion
Fecal diversion using loop ileostomy is a common protective measure to reduce symptoms of anastomotic leakage and better control of the leakages following sphincter-preserving operations such as low anterior resection for rectal cancer. (1–5) Resection with anastomosis (stapled or hand-sewn) of the ileum and direct repair of the ileum are the two major surgical techniques proposed for the ileostomy reversal. Although stapled anastomoses are becoming more popular among the surgeons, handsewn techniques, including resection or direct repair, have shown comparable results compared to the stapled technique. (25–27)

Few studies, mostly retrospective, have evaluated the impact of ileal resection on the outcome of the reversal of ileostomy. According to a retrospective study by D’Haeninck et al. (28), the incidence of postoperative complications, including prolonged ileus, bowel obstruction, anastomotic leak, and wound infection, were not influenced by the bowel resection during the closure. Similar results were found in a prospective non-randomized study done by Garcia-Botello et al. (29) In another retrospective study by Gustavsson et al. (21), there was no difference in terms of anastomotic leakage between the groups with and without bowel resection. However, median hospital stay was 6 and 5 days in the groups with and without resection, respectively. Phang et al. (23), in a retrospective analysis, demonstrated that bowel obstruction was significantly higher after closure using resection compared with the direct repair technique. According to the meta-analysis done by Madani et al. (30), bowel resection during the ileostomy reversal does not significantly increase the incidence of postoperative small bowel obstruction or anastomotic leakage.

Considering the effect of ileal resection on the bowel function after the operation, we found a significant difference between the two studied groups. In this clinical trial, the direct repair group (group A) revealed faster tolerance of diet at various levels. Bowel function returned more rapidly to normal in this group and they discharged earlier compared to group B. These can be justified as the lack of bowel resection in group A that may lead to a better function of the ileum after the operation. Intact intramural nervous system in the mesenteric side of the ileum in the direct repair group (group A) may be the reason for this better bowel function. However, signs or symptoms of complete or partial bowel obstruction did not develop in both groups during the early and late postoperative follow-up. Furthermore, intraoperative blood loss was significantly higher in group B, which can be due to the possible bleedings during the ligation of ileal mesenteric vessels. In the long-term, both groups revealed similar functions with no complications.

Although this study was the first randomized clinical trial published, the limited number of patients in both arms was the main drawback of it. Future studies with larger sample sizes to compare these two surgical techniques are recommended. Moreover, future clinical trials, including the stapled technique in addition to the hand-sewn technique, are suggested.

Conclusions
This study demonstrated that direct hand-sewn repair of the ileal defect is safe and rapid surgical techniques that can be used for the reversal of loop ileostomies created for the protection of low rectal anastomosis. Compared to the resection and hand-sewn anastomosis of the ileum, which is another common surgical technique in this regard, direct repair leads to a better bowel function and earlier discharge of the patient. However, major surgical complications, including early or late bowel obstruction, were not detected after both techniques.

**Declarations**

**Ethics approval and Consent to participate**

The study was approved by the *Research Ethics Committee of Tehran University of Medical Sciences* (27th August 2016). Permission to carry out the study and access patient records was sought from the respective university administrators (*Research department of Tehran University of Medical Sciences*). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants during data collection and confidentiality of the information was secured by omitting any identifiers from data.

**Consent for publication**

Not applicable.

**Availability of data and material**

The data that support the findings of this study are available from *Research department of Tehran University of Medical Sciences* but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of *Research department of Tehran University of Medical Sciences*.

**Competing interests**

The authors have no conflict of interest to declare.

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**Authors' contributions**

MK (Mohammadreza Keramati) and MM conceived and designed the study, MKa (Mohammadreza Karoobi) and MK collected the clinical data and MA carried out the data gathering. AK (Alireza Kazemeini),
AKe (Amir Keshvari) carried out the statistical analysis. MK and AKe drafted the manuscript and provided logistic support while BB, MS and MKa edited and prepared the final version of the article.

All author proofread and approved the final version of the manuscript.

Acknowledgments

None to declare

References


Figures
Figure 1

CONSORT flow diagram