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REVIEW ARTICLE

Bilateral vs. unilateral endoscopic ultrasound-guided celiac plexus neurolysis for abdominal pain management in patients with pancreatic malignancy: a systematic review and meta-analysis

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Abstract
Context Endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN) by bilateral or unilateral approach is widely used in palliative abdominal pain management in pancreatic cancer patients, but the analgesic effect and relative risks of the two different puncture routes remain controversial.
Objectives The aim of this systematic review was to evaluate the analgesic efficacy and safety of bilateral EUS-CPN compared with unilateral EUS-CPN.
Methods An electronic database search was performed for randomized controlled trials comparing bilateral and unilateral approaches of EUS-CPN using the Pubmed, Cochrane Library, Web of Science, Google Scholar, and CNKI databases. Meta-analysis was performed using RevMan 5.3 after screening and methodological evaluation of the selected studies. Outcomes included pain relief, treatment response, analgesic reduction, complications, and quality of life (QOL).
Results Six eligible studies involving 437 patients were included. No significant difference was found in short-term pain relief [SMD = 0.31, 95% CI (− 0.20, 0.81), $P = 0.23$] and response to treatment [RR = 0.99, 95% CI (0.77, 1.41), $P = 0.97$] between the bilateral and unilateral neurolysis groups. However, only the bilateral approach was associated with a statistically significant reduction in the postoperative use of analgesics [RR = 0.66, 95% CI (0.47, 0.94), $P = 0.02$] compared to the unilateral approach. A descriptive analysis was performed for complications and QOL.
Conclusion The short-term analgesic effect and general risk of bilateral EUS-CPN are comparable with those of unilateral EUS-CPN, but our evidence supports the conclusion that the bilateral approach significantly reduces postoperative analgesic use.

Keywords Endoscopic ultrasound · Celiac plexus · Neurolysis · Bilateral · Unilateral · Meta-analysis

Introduction

Pancreatic cancer is among the top 10 causes of cancer mortality in China [1], and its incidence has been rising at an annual rate of 1.2% from 2000 to 2012 in the USA [2] and Europe [3] with 7.6 males and 4.9 females affected per 100,000 individuals. The 5-year survival rate for pancreatic cancer is about 5–10%; for patients who qualify for surgical resection, the survival period is 12–15.9 months, and for those under conservative treatment, the average survival period is approximately 5.8 months [4–6]. A number of patients with pancreatic malignancy complain of pain at their first hospital visit. Pain usually occurs in the occult stage of the disease and gradually worsens as the disease progresses, and in the middle and late stages, this symptom is observed in about 90% patients [7]. Moreover, cancer pain markedly reduces the quality of life (QOL) and serves as a prognostic factor for survival [8, 9]. Therefore, palliative pain control is crucial in the context of advanced pancreatic cancer and ailments involving refractory chronic pain.

In recent years, celiac plexus neurolysis (CPN) under imaging-based visualization has gained prominence as a complementary approach to the three-step analgesic ladder pain

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management recommended by the World Health Organization. In fact, celiac plexus block was first used as an effective method to relieve pain as early as 1914; a study proposed that pancreatic cancer pain radiates through the celiac plexus into the central nervous system [10]. With the development of imaging technology, CPN has become more accurate and effective and is widely used in pain management.

In particular, endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN), by unilateral or bilateral approach, is accepted as a common measure for pain control in pancreatic cancer patients, with its advantages of real-time guidance, short puncture distance, use of the anterior pathway (avoiding puncture through the posterior diaphragm space), and color Doppler (avoiding vascular damage) [11, 12]. With reference to the different approaches, the bilateral approach is conducive to injection of medication at the bilateral diaphragmatic foot and both sides of the celiac trunk to produce analgesic effect on several ganglia [13] However, this approach is sophisticated, time-consuming, and requires higher skills, which could lead to higher risk.

Recently, randomized controlled trials and retrospective studies have been conducted on different puncture paths, while disagreement exists owing to the small number of individual reports. Therefore, this systematic review and meta-analysis compares the analgesic effect, medication reduction, and technology risk in bilateral and unilateral EUS-CPN treatment.

Methods

Search strategy and selection criteria

We performed a detailed electronic search using Pubmed Medline, Cochrane Library, Web of Science, Google Scholar, and CNKI databases using the search terms "pancreatic cancer," "abdominal cancer," "abdominal pain," "celiac plexus neurolysis," and "ultrasound-guided" for studies published between January 1997 and December 2016. The specific search strategy for Pubmed database is shown in Appendix. The following types of studies were selected: studies on chronic pain caused by abdominal malignancies or refractory pancreatitis, studies not limited to tumor staging, studies involving CPN guided by ultrasound endoscopic (EUS) technique, studies with a baseline pain score > 3, and randomized controlled trails (RCTs) or other well-designed clinical studies. Studies were excluded if invasive combination treatments, other imaging guidance methods (computed tomography), or other puncture pathways (percutaneous anterior or posterior approach) were used. Methodological evaluation for assessing risk of bias was performed in accordance with the Cochrane Collaboration's tool [14], and assessment was conducted on components of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias.

Data extraction and outcomes

A specific data extraction form was designed to acquire information on study authors, publication time, study type, patient characteristics, intervention methods, targets of injection, and outcomes. The primary outcome was visual analog scale (VAS) scores. Secondary outcome measures included response to treatment, reduction in analgesic use, adverse effects, and QOL. Data were screened independently by two researchers (Lu and Dong) in accordance with the inclusion and exclusion criteria and recorded using the extraction form. Disagreements were resolved by discussion and handed over to a third reviewer (Tang) for adjudication. In the event of incomplete data, we contacted the authors to obtain the required information. Original data were converted according to the Cochrane Handbook for Systematic Review of Interventions [15] to meet statistical requirements when inconsistencies were found in unit or statistical expression. Two studies [13, 16] used the numerical rating scale (NRS) to evaluate pain intensity, and we converted the data to VAS scores, and all continuous variables [13, 17] were represented as means and standard deviations.

Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) version 5.3 (The Cochrane Collaboration, Copenhagen, DK) and SPSS version 19.0 software (SPSS Inc., Chicago, USA). Continuous variables (response to treatment, analgesic medicine reduction) were calculated as relative risk (RR) and VAS scores were assessed as standardized mean difference (SMD), both with a 95% confidence interval (CI). Heterogeneity of the selected studies was calculated using the chi-square test and measured using I^2. The heterogeneity was considered significant if $P \leq 0.10$ or $I^2 < 50\%$, in which case, the possible causes of heterogeneity were analyzed and a random effects model was used; otherwise, a fixed effects model was chosen. Descriptive qualitative analysis was used when meta-analysis could not be conducted because of incomplete data.

Results

Identification of eligible studies

In total, 742 articles were identified using database and reference searches, 35 of which were deemed eligible for full-text assessment after screening titles and abstracts and excluding duplicate publications (Fig. 1). Of the 35 studies, 14 were

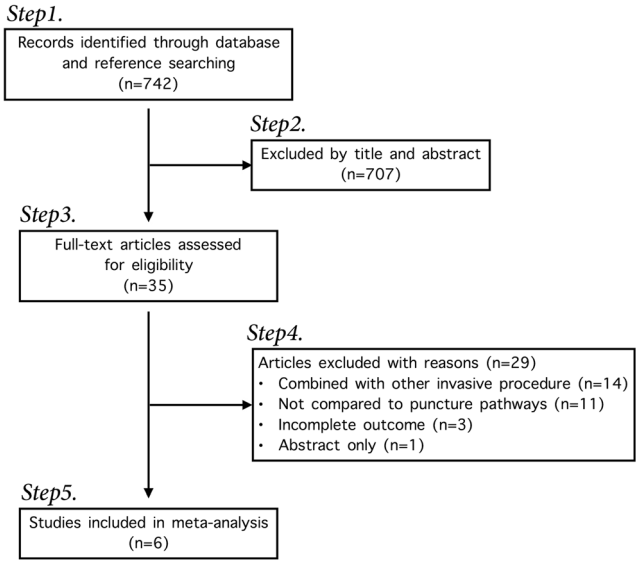

Fig. 1 Flow chart of study selection

excluded because they were combined or compared with other invasive neurolysis techniques apart from EUS-CPN. Eleven studies were excluded because no comparison was made between unilateral and bilateral approaches; four contained incomplete data, and we were unable to contact the authors for more information. Therefore, a total of six studies were included in our meta-analysis.

Characteristics of included studies

All of the six included studies, published between 2009 and 2014, reported the use of EUS-guided bilateral and unilateral CPN for refractory abdominal pain caused by pancreatic malignancy or chronic pancreatitis. Three studies were from the USA, and the other three were from Canada, Mexico, and India. In total, 437 patients were enrolled in these studies, including 160 patients from three RCTs, 117 from two retrospective analyses, and 160 from a prospective cohort study. Alcohol was used as the neurolysis agent in all the studies except for one [18] in which bupivacaine was used in the celiac plexus block for pancreatitis-induced abdominal pain. Outcomes including pain intensity assessed by VAS or NRS, treatment response, medication reduction, and side effects were reported in all studies. In addition, patient satisfaction, survival, and QOL were analyzed using LeBlanc and Bhatnagar's methods [13, 16]. Further, characteristics of the included studies are shown in Table 1.

Methodological evaluation of included studies

Table 2 shows the results of methodological quality assessment of the included studies, all of which reported the patients' baseline conditions and had complete data. For random sequence generation, two studies [13, 18] used the Rand table, and one study [16] used computerized random numbers. Envelopes were reported in two studies [13, 18] for allocation concealment. All randomized controlled studies and prospective cohort studies used correct blinding methods.

Impact on pain relief

Four studies [13, 16, 17, 19] reported changes in pain level after EUS-CPN, of which two [13, 16] used NRS data which we converted to VAS scores. The time points for assessment in this systematic review were 1 week after surgery, and some studies [16, 17] reported VAS scores at 1 and 3 months postsurgery. However, because of the small number of reports, we could not perform meta-analysis. Heterogeneity of the eligible studies was found to be statistically significant ($P = 0.02$, $I^2 = 71\%$). The possible reason for heterogeneity was believed to be the subjectivity VAS owing to different geographical backgrounds and health education, which may influence comprehension of pain. However, this did not affect

Table 1 General characteristics of included studies

Study	Country	Design	Number of patients		Subjects		Agents	Outcome
			Bilateral	Unilateral	M/F	Age		
Ascunce (2011)	USA	Retrospective	24	40	28/36	63.4 (11.7)	98% alcohol	VAS, response, narcotic dosage, adverse effect
LeBlanc (2009)	USA	RCT	27	23	20/30	43 (40.7)	0.75% bupivacaine	VAS, pain relief, medications, satisfaction
LeBlanc (2011)	USA	RCT	21	29	24/26	62.9 (11.5)	98% alcohol	NRS, pain relief, medications, survival
Bhatnagar (2014)	India	RCT	30	30	23/37	46.8 (12.4)	50% alcohol	NRS, response, medications, QOL, complication
Téllez-Ávila (2013)	México	Retrospective	32	21	24/29	59 (40.7)	98% alcohol	VAS, response, medications, complication
Sahai (2009)	Canada	Cohort study	89	71	78/82	55.2 (–)	Absolute alcohol	VAS, response, medication, complication

Table 2 Assessment in methodological quality of included trials

Study	Sequence generation	Allocation concealment	Blinding	Data integrity	Selective reporting	Other bias
Ascunce (2011)	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
LeBlanc (2009)	Envelopes	Envelopes	Low risk	Low risk	Low risk	Low risk
LeBlanc (2011)	Rand table	Envelopes	Low risk	Low risk	Low risk	Low risk
Bhatnagar (2014)	Computer	Unclear	Low risk	Low risk	Low risk	Low risk
Téllez-Ávila (2013)	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Sahai (2009)	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear

assessment of the difference in pain level between the experimental and control groups. The results were obtained using a random effects model [SMD = 0.31, 95% CI (− 0.20, 0.81), $P = 0.23$], suggesting that there was no significant difference in pain relief at 1 week with the use of either bilateral or unilateral neurolysis (Fig. 2).

Impact on treatment response

All of the six studies reported response to treatment, and although Bhatnagar [16] used continuous variables (NRS, 0–100) to assess the intensity of treatment response, data in the other five studies [13, 17–20] were presented using dichotomous variables and reviewed systematically. The heterogeneity test showed statistically significant differences ($P = 0.003$, $I^2 = 75\%$) among the groups, which may be attributable to differences in the definition of response in each study. A random effects model was used, and no significant difference in response to treatment was found between the bilateral and unilateral approach [RR = 0.99, 95% CI (0.77, 1.41), $P = 0.97$] (Fig. 3).

Reduction in postoperative use of analgesics

Four studies [13, 16, 18, 19] assessed the use of pain medicine before and after treatment and reported differences between unilateral and bilateral approaches. The heterogeneity test showed no heterogeneity among studies ($P = 0.13$, $I^2 = 47\%$), and this was also confirmed by symmetry in the funnel plot (Fig. 4). Therefore, a fixed effects model was chosen. The results showed a statistically significant difference in analgesic reduction (RR = 0.66, 95% CI (0.47, 0.94), $P = 0.02$), indicating that analgesic usage reduced significantly after the bilateral procedure compared to the unilateral procedure (Fig. 5).

Complications and the quality of life

Complications were reported in all six studies, but only two studies [16, 20] compared the differences between the two puncture routes. In Bhatnagar's study [16], the incidences of diarrhea and hypotension in the bilateral and unilateral groups were 10 (0.33) vs. 12 (0.4) and 3 (0.1) vs. 4 (0.13), respectively, with no significant difference. One case of self-limited retroperitoneal bleeding in bilateral neurolysis was reported [20]. Other complications included 20 cases of postprocedural pain, 15 cases of transitory self-limited loose stools, and one case of mild pancreatitis after biopsy. Bhatnagar evaluated the QOL using the discomfort score (0–5) [16], which included bowel function, self-care, maintaining personal hygiene, eating, interacting with family, and ambulation, and the results showed no significant difference between the two groups at 3 months, with the score being 3.20 (0.99) vs. 2.23 (0.77). The survival period of the patients was 35.0 [95% CI (20.0, 49.4)] and 25.3 [95% CI (15.7, 29.0)] weeks following EUS-guided bilateral and unilateral CPN, respectively [13].

Discussion

The celiac plexus is the largest autonomic nerve plexus, consisting of the celiac ganglion, the renal ganglion, and the superior and inferior mesenteric ganglia. It is located

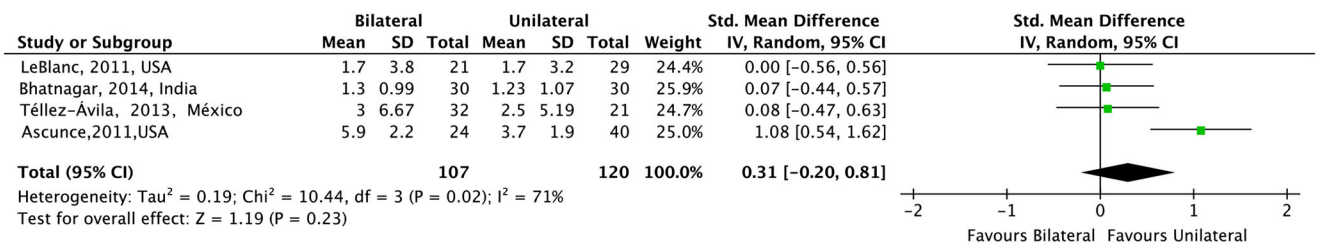

Fig. 2 Pain relief assessment using VAS at 1 week; std. mean difference, standardized mean difference; CI, confidence interval

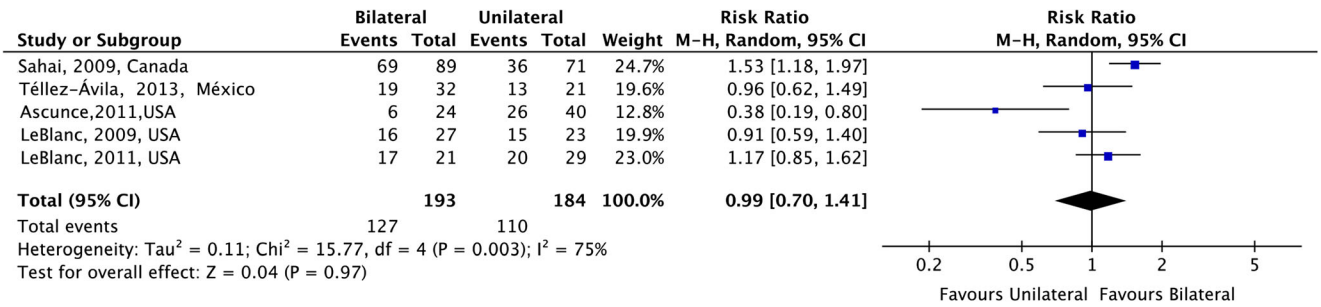

Fig. 3 Forest plot of response to treatment; CI, confidence interval

in the anterior or lateral abdominal aorta, around the celiac trunk and superior mesenteric artery takeoff at the T12–L1 level and is the interconnecting network for the visceral sympathetic and parasympathetic nerves [21–23]. The celiac plexus can be clearly marked when the takeoff of the celiac trunk and superior mesenteric artery are scanned using an ultrasound endoscope. Therefore, the primary advantages of EUS-CPN are short puncture path and real-time guidance, and the National Comprehensive Cancer Network guidelines for pancreatic adenocarcinoma recommend this procedure for pain control, especially in patients with unresectable lesions at surgery [24]. However, EUS-CPN is not yet widely used in pain clinics because the efficacy and safety outcomes are largely operator-dependent, and supportive evidence is still insufficient compared to the percutaneous technique.

The analgesic effect of EUS-CPN is well correlated with the distribution of the injected medication. An optimal block can be achieved when the medication is distributed on both sides of the abdominal aorta and spread over the retroperitoneal space between T11 and L2 [25, 26]. Thus, bilateral puncture, with the target on both sides of the celiac trunk takeoff, is believed to block more ganglia and achieve wider diffusion of medication, resulting in

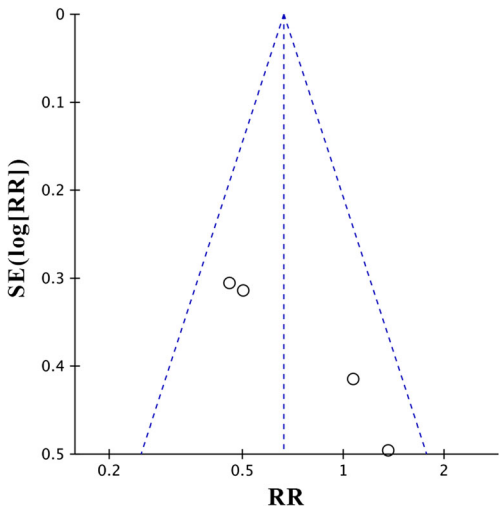

Fig. 4 Funnel plot of analgesic reduction indicating no evidence of bias of included studies; RR, relative risk

superior pain relief. However, our systematic review found that EUS-guided bilateral neurolysis was comparable to the unilateral approach in early postoperative pain relief. Several studies [27–29] reported that the effective success rate of CPN was 50–70%, and the analgesic effect lasted for an average of 3 and up to 6 months. Similarly, studies included here also reported a significant decrease in cancer pain level with the majority of patients responding positively to treatment, but there was no significant difference between the two procedure routes.

We also note some limitations of this study including the use of VAS scores for assessing heterogeneity and response to treatment. The subjectivity of VAS assessment and difference in the definition of treatment response may have resulted in high heterogeneity, and most investigators [13, 17, 18, 20] define 30–50% VAS decline from baseline as a positive indicator. In addition, due to incomplete data at 1 and 3 months, we could only perform a meta-analysis of the data at an early stage (1 week) after operation.

The bilateral approach is difficult to perform, and it may cause left adrenal artery injury or could be impeded by tumor infiltration or enlarged lymph nodes [20]. In addition, a hyperechoic image of the target structure is acquired after alcohol injection, which may reduce the accuracy of a second puncture approach under ultrasound guidance [13]. Accordingly, the risk of bleeding, puncture injury, and infection may increase with repetition of the procedure. However, the overall complications identified in our study were mild, including hypotension, postprocedural pain, and diarrhea. In fact, some of the reported complications (hypotension and diarrhea) are cardinal signs of successful sympathetic block, rather than actual complications. Although the incidence of diarrhea and hypotension is different between the bilateral and unilateral groups, the surgical approach is not responsible for this variance. In fact, the symptoms of sympathetic block are expected, and they essentially depend on the total amount of medication around the target.

Reduction in analgesic use was reported in all the included studies. In our systematic review, the bilateral procedure was associated with a statistically significant reduction in analgesic usage compared to the unilateral approach. This finding led us to another perspective; greater analgesic reduction in the

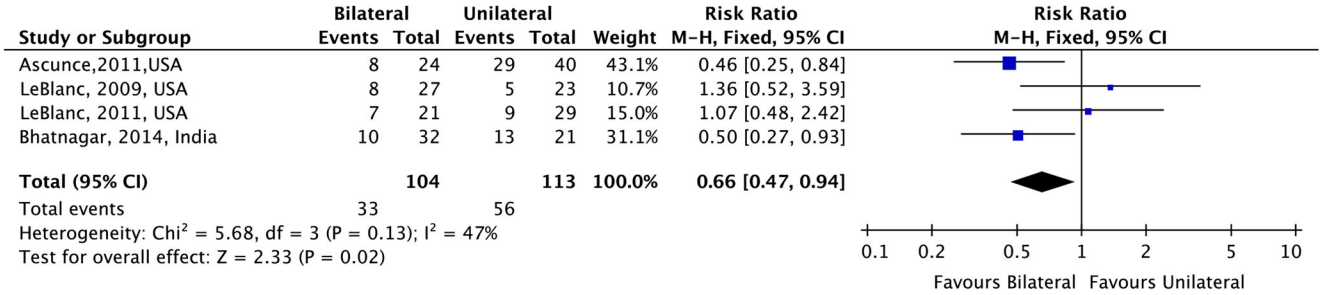

Fig. 5 Forest plot of analgesic reduction; CI, confidence interval

bilateral group revealed that this approach may be more effective than the unilateral approach, although the pain score was comparable between the two groups because the total pain score may be influenced by the medication after CPN. However, withdrawal of medication is clearly not the main purpose of chronic malignant pain management. The aim of EUS-CPN is to enable patients to achieve better pain relief and reduce dose-dependent complications such as constipation, nausea, vomiting, and dizziness caused by opioids, NSAIDs, and anticonvulsant analgesics. Recently, Wang et al. [30] reported that patients with pancreatic carcinoma experienced significant pain relief and reduction in analgesic use 2 weeks after implantation of ^{125}I seeds in the celiac plexus under EUS guidance. With the development of novel strategies, combined therapy can be actively considered in palliative pain management, provided the benefits are carefully contemplated in advance.

In conclusion, EUS-guided bilateral CPN is comparable with the unilateral approach in terms of overall pain relief, but it is associated with a significant reduction in analgesic consumption. There is insufficient evidence to support a greater risk in bilateral EUS-CPN.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Appendix

Search strategy for Pubmed database

1 Pancreatic cancer or pancreatic neoplasms
2 Pancreatic and neoplasms
3 Pancreatic and cancer
4 1 or 2 or 3
5 Celiac plexus
6 Coeliac plexus
7 Celiac and plexus
8 Neurolysis
9 5 or 6 or 7
10 9 and 8
11 4 and 10
12 Abdomen or abdominal
13 Neoplasms or cancer
14 12 and 13
15 10 and 14
16 Abdominal pains
17 Abdominal and pain
18 12 or 13
19 10 and 18
20 Ultrasound or ultrasonography or ultrasonic
21 Diagnostic imaging
22 Diagnostic and imaging
23 Guided
24 20 or 21 or 22
25 24 and 23
26 Limit 11 to humans
27 Limit 15 to humans
28 Limit 19 to humans
29 Limit 25 to humans
30 26 and 29
31 26 and 29
32 28 and 29

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