ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ИСКУССТВЕННОЙ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ В УСЛОВИЯХ РЕАЛЬНОЙ ЖИЗНИ У ДЕТЕЙ С САХАРНЫМ ДИАБЕТОМ 1 ТИПА: СИСТЕМАТИЧЕСКИЙ ОБЗОР

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ОБОСНОВАНИЕ. В последние годы проведены многочисленные пилотные и клинические исследования с применением систем с закрытым контуром управления гликемией, в том числе с участием детей и подростков в условиях, максимально приближенных к реальной жизни пациентов.

ЦЕЛЬ. Сравнить эффективность и безопасность применения систем с замкнутым контуром управления гликеми-ей у детей и подростков с сахарным диабетом 1 типа в условиях, максимально приближенных к реальной жизни, по сравнению с традиционной помповой инсулинотерапией (с непрерывным мониторированием гликемии или без) на основе результатов проведенных рандомизированных клинических исследований (РКИ).

МЕТОДЫ. В систематический обзор включены результаты 28 РКИ, опубликованные до 15 июня 2017 г. и проиндексированные в базе MEDLINE. Для сравнения эффективности оценивалось время нахождения гликемии в диапазоне от 3,9 до 10 ммоль/л, а также медиана гликемии и ее вариабельность по данным непрерывного мониторирования. Безопасность сравнивалась по продолжительности гипогликемий (времени нахождения гликемии в диапазоне <3,9 ммоль/л).

РЕЗУЛЬТАТЫ. Во всех исследованиях отмечалось значительное увеличение времени нахождения гликемии в целевом диапазоне в ночном интервале. В 3 РКИ при анализе всех суток показано снижение доли времени нахождения гликемии в целевом диапазоне. Только одно РКИ показало статистически значимое различие между моногормональной и бигормональной системой в отношении времени, проведенного в целевых значениях. Средняя гликемии и показатели вариабельности гликемии в исследованиях изменялись разнонаправленно, как при оценке в ночном интервале времени, так и при оценке за все сутки. Продолжительность гипогликемий в ночное время в большинстве РКИ значимо снизилась, и только в 2 РКИ зафиксировано увеличение времени нахождения гликемии в диапазоне <3,9 ммоль/л, в одном РКИ не было отмечено различий с традиционной помповой инсулинотерапией. При оценке гликемии за сутки продолжительность гипогликемий в разных РКИ изменялась разнонаправленно. Различная методология оценки гликемического контроля и небольшая продолжительность РКИ не позволили провести метаанализ результатов и реализовать количественное их обобщение.

ЗАКЛЮЧЕНИЕ. Большинство РКИ свидетельствуют о преимуществах систем с замкнутым контуром управления гликемией перед традиционной помповой инсулинотерапией в отношении эффективности и безопасности у детей с сахарным диабетом 1 типа в условиях повседневной жизни. Необходимо проведение более длительных РКИ с унифицированной оценкой эффективности и безопасности, а также анализом кумулятивных показателей (в том числе – HbA_{1c}) для получения убедительных доказательств наличия или отсутствия преимуществ систем с замкнутым контуром управления гликемией перед традиционной помповой инсулинотерапией.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 1 типа; дети; подростки; искусственная поджелудочная железа; помповая инсулинотерапия; замкнутый контур; рандомизированные клинические исследования; систематический обзор.

FREE-LIVING USE OF ARTIFICIAL PANCREAS FOR CHILDREN WITH TYPE 1 DIABETES: SYSTEMATIC REVIEW

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BACKGRAUND: A closed-loop glucose control system or 'artificial pancreas' consists of three components – a Continuous Glucose Monitor (CGM), infusion pumps to deliver hormone(s) and a sophisticated dosing algorithm to control hormone delivery. In the past years, numerous studies with closed-loop system devices were conducted with gradual shift to out-of-hospital environment and with lengthening study duration.

AIMS: To compare efficacy and safety of closed-loop insulin pump use in children with type 1 diabetes mellitus in compare with conventional insulin treatment (continuous subcutaneous insulin infusion (CSII) with our without CGM) based on randomized control trials data (RCT).

METHODS: In the systematic review we have include 28 randomized controlled trials results indexed in PubMed, Medline databases published till 15 June 2017. The efficacy on metabolic control in this study evaluated by the proportion of time within target range (preferably 70 to 180 mg/dl if reported) and mean (median) glucose based on sensor measurements, and the safety evaluated by time in hypoglycemia (below 70 mg/dl if reported).

RESULTS: Increased time in range in the night period was observed in all RCT. Only 3 RCT showed decrease of the time in range within 24 h evaluation period. In one RCT the significant positive differences have been shown in the time in range for dual hormone closed-loop glucose control system in compare with insulin-only artificial pancreas. Mean glycaemia and glucose variability changes were not in the same manner in different RCT, both in the night only and in 24 h estimation period. Night hypoglycemia duration decreased in most RCT with closed-loop control in compare with CSII, and increased only in 2 RCT. When all-day estimation period the time in hypoglycemia changed not in the same manner in different RCT. Valuable methodology differences of the glycaemic control estimation within observed RCT brought significant complications in the data analysis and made impossible the results quantitative estimation to prepare a metaanalysis.

CONCLUSIONS: Much work has been done to develop effective and safe artificial pancreas, but not all RCTs confirmed advantages of closed-loop glucose control in compare with CSII in children and adolescents in real life. More research with prospective randomized control design required to prove benefits of closed-loop glucose control. Further RCTs should have an uniform methodology for glycemic control assessment and long duration that will allow to use cumulative measures in a closed-loop efficacy estimation (HbA_{1c}).

KEYWORDS: Diabetes Mellitus, Type 1; Insulin Infusion Systems; Pancreas, Artificial; Closed-Loop; CSII; CGM; sensor augmented pump; systematic review; randomized control trial; children

INTRODUCTION

Precise glucose control is crucial for patients with type 1 diabetes [1]. More than 20 years ago results of Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study of the DCCT cohort showed that most people with type 1 diabetes should be treated intensively to achieve glycated hemoglobin A1c (HbA1c) levels as close to normal as possible and as early as possible in the course of the disease to prevent or postpone the late disease complications [2]. Consequently, intensive day-to-day management remains the standard of care in type 1 diabetes management recommendations [3]. However, an up-to-date data based on national registries show that an important proportion of the patients worldwide do not reach the goal of desired metabolic control [4–7], which is HbA1c below 7.0% (53 mmol/ mol) for adults [8] and below 7.5% (58 mmol/mol) for children and adolescents [9, 10]. There is a strong surge for technologies that could provide intensive insulin therapy and thereby improve metabolic control and at the same time minimizing glucose excursions that can be harmful for developing brain structure [11–13].

Continuous glucose monitoring (CGM) can enable patients, their families and care-givers as well as clinicians to make better-informed decisions on how to control blood glucose levels, but only when this is fully adopted in day-to-day care [14, 15]. Improvements in recent years have allowed for better accuracy and simplicity of CGM use, and, consequently, more successful implementation [16], effective also with non-adjuvant use [17, 18]. Sensor-augmented insulin pump therapy and threshold-suspend features added to CGM may additionally reduce the burden of hypoglycemia and increase time in target range, but there is limited effect on time in hyperglycemia [19].

A closed-loop system or artificial pancreas consists of three components – a CGM, infusion pumps to deliver hormones, and a sophisticated dosing algorithm [20, 21] to control single (insulin) our dual (insulin and glucagon – also called bihormonal or bionic system) hormone delivery. In the past years, numerous studies with closed-loop system devices were conducted with gradual shift to out-of-hospital environment and with lengthening study duration.

With the present review we are outlining data from randomized controlled trials with out-of-hospital closed loop glucose control for patients with type 1 diabetes.

DATA SOURCE

We searched PubMed from database inception until 15th of July, 2017, using the search terms and medical subject headings (MeSH) artificial pancreas OR closed-loop OR closed loop in outpatient setting (home OR outpatient OR camp OR hotel) in patients with type 1 diabetes for reports of randomized controlled trials. References and related citations of articles were screened to identify other relevant articles. To be included into the review, studies had to be RCTs comparing closed-

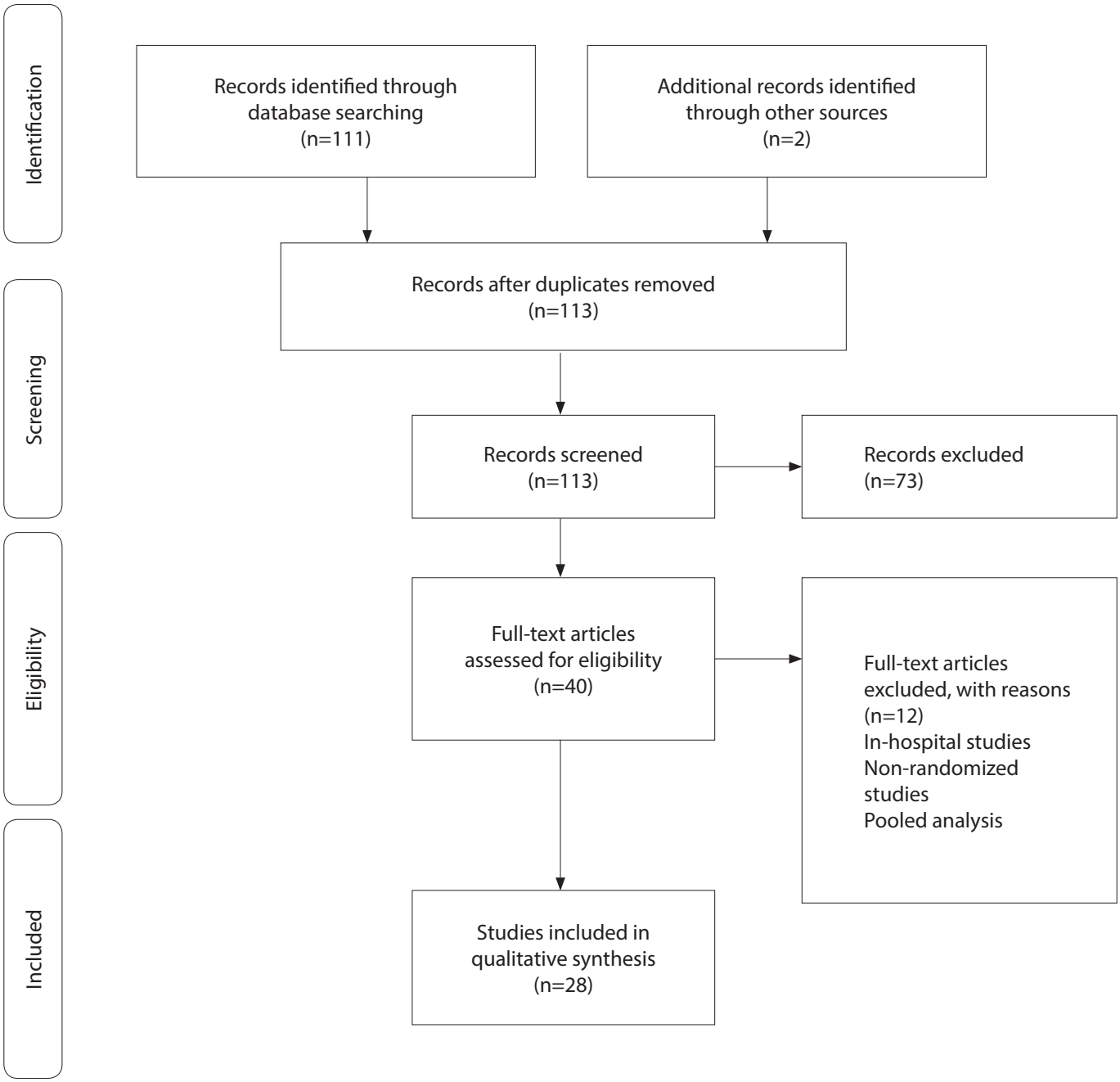

Figure 1. Study flowchart for selection of trials for inclusion.

loop use with conventional insulin treatment (CSII with our without CGM) and the study aim to achieve an improvement in metabolic control with reported glycemic outcomes analysis. The primary endpoint of this review was proportion of time within target range (preferably 70 to 180 mg/dl if reported, additionally we looked also into time in hypoglycemia (below 70 mg/dl if reported) and mean (median) glucose based on sensor measurements [22]. In present review we followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement and checklist.

RESULTS

We present search results, number of trials reviewed and selected in Figure 1. Twenty-nine reports on 28 randomized controlled trials containing and analyzing data on 739 adults, children and adolescents with type 1 diabetes were included into this review (Table 1). Thirteen comparisons evaluated glycemic control for the overnight period, in 14 trials the observational period was both day and night, one trial evaluated day and night glycemic control for the adult population and overnight for pediatric population. In 15 RCTs the model predictive control (MPC) algorithm was used, proportional integrative derivative (PID) in nine, four used fuzzy logic algorithm driven closed-loop. Clinical trials were diverse in number of patients included (from eight to 75), duration of observational period (from one night to 12 weeks), clinical setting (camp, hotel, at home) and included participant's average age. Two clinical trials appraised both dual and single hormone system in a three-way comparison, five trials evaluated dual hormone system use, and all the other trials appraised single hormone system. The usual comparator was sensor augmented pump (SAP), in three trials with low glucose suspend (LGS) function turned on, in all three the comparator was single hormone system.

Table 1. Overview of glycemic control for randomized controlled trials on outpatient use of closed-loop in type 1 diabetes by years and observational period

OVERNIGHT STUDIES

Year	First author (Ref.)	Participants (n)	Age (mean)	Study duration	Intervention	Study outcomes	Outcome difference: Intervention vs. Control	P value
2013	Philip [23]	54	13.8	1 night	Fuzzy Logic/Single	Time in target range	1.4 (h)	<0.05
						Time in hypoglycemia	0%	0.02
						Mean glucose	-14 mg/dL	<0.05
2014	Hovorka [24]	16	15.6	3 weeks	MPC/Single	Time in target range	15%	<0.001
						Time in hypoglycemia	-7%	<0.01
						Mean glucose	-14 mg/dL	<0.001
2014	Nimri [25]	21	21.2	6 weeks	Fuzzy Logic / Single	Time in target range	21.8%	0.003
						Time in hypoglycemia	-40.2%	0.020
						Mean glucose	-15 mg/dL	0.008
2014	Nimri [26]	15	19.0	4 nights	Fuzzy Logic / Single	Time in target range	1.3 h	0.0479
						Time in hypoglycemia	-44.9 min	0.0034
						Median glucose	3.5 mg/dL	0.8148
2014	Ly [27]	20	15.3	5-6 nights	PID / Single	Time in target range	7%	0.233
						Time in hypoglycemia	/	/
						Mean glucose	1 mg/dL	0.887
2014	Thabit [28]	24	43	4 weeks	MPC / Single	Time in target range	12%	0.0004
						Time in hypoglycemia	-0.3%	0.28
						Mean glucose	-14.4 mg/dL	0.0052
2015	Brown [29]	10	46.4	5 nights	PID / Single	Time in target range	26.30%	<0.001
						Time in hypoglycemia	-0.99%	NS
						Mean glucose	-31.3 mg/dL	<0.001
2015	Haidar [30]	33	13.3	3 nights	MPC / Dual / Single	Time in target range		
						Dual CL vs. SAP	33%	<0.001
						Single CL vs. SAP	16%	0.0003
						Time in hypoglycemia		
						Dual CL vs. SAP	-1.7%	0.0048
						Single CL vs. SAP	0%	0.32

Year	First author (Ref.)	Participants (n)	Age (mean)	Study duration	Intervention	Study outcomes	Outcome difference: Intervention vs. Control	P value
2015	Kropff [31]	32	47	12 weeks	MPC / Single	Time in target range	8.6%	<0.0001
						Time in hypoglycemia	-1.0%	0.00022
						Decrease in HbA1C	-0.3%	0.047
2015	Thabit [32] (children)	25	12	12 weeks	MPC / Single	Time in target range	8.9%	<0.001
						Time in hypoglycemia	0.82%	0.18
						Mean glucose	-9 mg/dL	0.01
2016	Haidar [33]	28	33.3	2 nights	MPC / Dual / Single	Time in target range		
						Dual CL vs. SAP	22%	<0.001
						Single CL vs. SAP	15%	<0.001
						Time in hypoglycemia		
						Dual CL vs. SAP	-7 %	<0.001
						Single CL vs. SAP	6 %	0.004
2016	Ly [34]	21	14.7	5-6 nights	PID / Single	Time in target range	15.8%	0.0038
						Time in hypoglycemia	14.1%	0.0011
						Mean glucose	4	0.6494
2016	Sharifi [35]	28	42 (adults) 15.2 (children)	4 nights	PID / Single Vs. LGS	Time in target range	6.2%	0.13
						Time in hypoglycemia	1.1%	<0.001
						Mean glucose	2.0 mg/dl	0.68
2017	Nimri [36]	75	19.5	4 nights	Fuzzy Logic / Single	Time in target range	13.5%	0.001
						Time in hypoglycemia	-0.53%	0.004
						Mean glucose	-7.9 mg/dl	0.334

DAY AND NIGHT OBSERVATIONAL PERIOD

Year	First author (Ref.)	Participants (n)	Age (mean)	Study duration	Intervention	Study outcomes	Outcome difference: Intervention vs. Control	P value
2014	Leelarathna [37]	17	34	16 days	MPC / Single	Time in target range	13%	0.005
						Time in hypoglycemia	1.3%	0.339
						Mean glucose	-12.6 mg/dL	0.027
2014	Kovatchev [38]	18	46	80 h	PID / Single	Time in target range	-4.6%	>0.1
						Time in hypoglycemia	-0.55%	>0.1
						Mean glucose	9 mg/dL	<0.04

Year	First author (Ref.)	Participants (n)	Age (mean)	Study duration	Intervention	Study outcomes	Outcome difference: Intervention vs. Control	P value
2014	Russell [39]	52	56 (adults) 16 (children)	5 days	MPC / Dual	Time in target range	20.7% (adults) 11.4% (children)	<0.001 <0.001
						Time in hypoglycemia	-3.2% (adults) -1.8% (children)	0.01 0.05
						Mean glucose	-26 mg/dL (adults -16 mg/dL (children)	<0.01 0.04
2015	Thabit [32] (Adults)	33	40	12 weeks	MPC / Single	Time in target range	11%	<0.001
						Time in hypoglycemia	0.8%	0.02
						Mean glucose	-11 mg/dL	<0.001
2015	Ly [40]	20	18.6	6 days	PID / Single Vs. LGS	Time in target range	-3.2%	0.580
						Time in hypoglycemia	-0.3%	0.656
						Mean glucose	10 mg/dL	0.274
2015	De Bock [41]	8	Unknown	5 days	PID / Single Vs. LGS	Time in target range	6.4%	0.30
						Time in hypoglycemia	0.1%	0.84
						Median glucose	-12.6 mg/dL	0.86
2016	Blauw [42]	10	41	3 days	PID / Dual	Time in target range	16.2%	0.007
						Time in hypoglycemia	-1.1%	0.139
						Median glucose	-7.2 mg/dL	0.123
2016	Russell [43]	19	9.8	5 days	MPC / Dual	Time in target range	23%	<0.0001
						Time in hypoglycemia	1.6%	<0.0001
						Mean glucose	-30.6 mg/dL	0.00037
2016	Tauschmann [44]	12	14.6	3 weeks	MPC / Single	Time in target range	18.8%	<0.001
						Time in hypoglycemia	0.4%	0.33
						Mean glucose	-32.4 mg/dL	0.001
2016	Del Favaro [45]	30	7.6	72 h	MPC / Single	Time in target range	-6.3%	0.022
						Time in hypoglycemia	-4.7%	<0.001
						Mean glucose	12 mg/dL	<0.001
2016	Tauschmann [46]	12	15.4	7 days	MPC / Single	Time in target range	19%	<0.01
						Time in hypoglycemia	1.2%	0.87
						Mean glucose	-25.2 mg/dL	0.028

Year	First author (Ref.)	Participants (n)	Age (mean)	Study duration	Intervention	Study outcomes	Outcome difference: Intervention vs. Control	P value
2017	El Khatib [47]	43	33.3	11 days	MPC/Dual	Time in target range	16.5%	<0.0001
						Time in hypoglycemia	-1.3%	<0.0001
						Mean glucose	-19.8 mg/dL	<0.0001
2017	Haidar [48]	23	41	60 h	MPC/Dual	Time in target range		
						Dual CL vs. SAP	3.2%	0.31
						Single CL vs. SAP	3.0%	0.41
						Time in hypoglycemia		
						Dual CL vs. SAP	-4.0%	0.002
						Single CL vs. SAP	-3.4%	0.001
						Time in target range	26%	<0.001
2017	De Boer [49]	12	7	3 days	PID/Single	Time in hypoglycemia	-0.5%	NS
						Mean glucose	-38 mg/dL	<0.001
2017	Bally [50]	28	41	4 weeks	MPC/Single	Time in target range	10.6%	<0.0001
						Time in hypoglycemia	-2.4%	<0.0001
						Mean glucose	-7.2 mg/dL	0.0226

Comments: LGS – low glucose suspend, MPC - model predictive control, NS – not significant, PID – proportional integrative derivative, SAP – sensor augmented pump

TIME IN TARGET GLYCEMIC RANGE

The first RCT contrasted single hormone closed-loop control with SAP in outside hospital settings in 2013, including 54 adolescents with type 1 diabetes [23]. Median time (IQR) within range 70 to 140 mg/dl for the overnight period was 4.4 (2.8 to 6.7) hours with closed-loop compared to 2.8 (1.5 to 4.4) hours with SAP ($p<0.05$).

In next four years additional eleven trials including 348 participants evaluated overnight glycemic control with single hormone closed-loop control. In all but two there was a significant improvement in time spent in target range (Table 1).

From the year 2014 several trials with single-hormone closed-loop control evaluation and 24/7 observational period showed significant improvement in time spent within target range [31, 32, 37, 44–46]. Out of those, Thabit and colleagues reported the longest randomized out of hospital study to date. Participants including both adults (evaluated for day and night period) and children (only overnight period) that were evaluated for 12-week period with closed-loop and than sensor-augmented pump glucose control or other way around. Among both adults and children the percentage of time when the glucose was within target range was increased with closed-loop glucose control (for adult population with paired difference 11%, $p<0.001$ and with 8.9 %,$p<0.001$ for children) [32].

Additional three trials compared closed-loop glucose control to LGS feature enabled SAP [35, 40, 51], none showed improvement in time spent within range.

Seven trials including 101 children and adolescents and 117 adults contrasted the use of dual hormone closed-loop with SAP in outpatient setting. Six out of seven trials revealed a significant increase in time spent within target range [30, 33, 39, 42, 43, 47].

Three trials had a three-way comparison design between dual-hormone (insulin and glucagon) closed-loop, single-hormone closed-loop and conventional insulin pump therapy. Only one of them showed a significant difference between dual-hormone single-hormone closed-loop glucose control in terms of time spent within target range ($p=0.032$) [30].

To date only two outpatient day-and-night trials evaluated the use of closed-loop in young preadolescent children [43, 45]. These two studies included 19 and 30 children aged 6-11 years and 5-9 years, respectively. In the former trial the use of dual-hormone closed-loop resulted in a significant improvement in time spent within target range comparing SAP ($p<0.0001$) [43]. Similarly, the second one showed a significant ($p=0.022$) improvement in

the percentage of time spent in target range with single-hormone closed-loop glucose control [45].

TIME SPENT IN HYPOGLYCEMIA

In nine out of ten outpatient RCTs single-hormone closed loop glucose control reduced time spent in hypoglycemia (Table 1). The difference between two treatment modalities was less pronounced for the 24/7 observational period where only three trials reported reduced time spent hypoglycemia during single-hormone closed-loop use [31, 32, 45].

Compared to LGS enabled feature treatment group single-hormone closed-loop use improved time in hypoglycemia in one out of three trials [35].

For the subgroup of trials with dual-hormone systems closed-loop insulin-delivery reduced time spent in hypoglycemia ($p=0.048$, $p<0.01$, $p<0.0001$, $p<0.0001$, $p=0.017$) in five RCTs [33, 43, 47, 48, 52], in one trial including both adult and adolescent population the percentage of time in hypoglycemia was reduced in adult population ($p=0.001$), but not among adolescents ($p=0.23$) [39]. Likewise, another dual closed loop study failed to show a significant difference ($p=0.139$) in the percentage of time spent in hypoglycemia [42]. In a three way comparison dual-hormone system improved time spent in hypoglycemia below 76 mg/dl ($p=0.032$) in one of three RCTs comparing single-hormone closed-loop use [30].

MEAN GLUCOSE AND GLUCOSE VARIABILITY

Nine trials (four for overnight and five for 24/7 evaluation) with single-hormone and additional four with dual-hormone use showed a significantly reduced mean (median) glucose during single-hormone closed-loop (Table 1). In two trials mean glucose was increased [38, 45] and in other seven there was no difference between the treatment groups, including the comparison between single and dual-hormone system (Table 1).

To date, several trials comparing closed loop with SAP reported significantly lower glucose variability [23, 25, 31, 32, 37]. However, no significant decrease was showed in eight additional trials including 202 participants [28, 29, 34, 36, 38, 45, 46], and a trial conducted on 16 adolescents reported an increase of 3% in glucose variability within each night ($p<0.003$) [24]. Compared to LGS system closed-loop glucose control reduced glucose variability in one trial [35], in other two this glucose outcome was not reporeted.

Similar observations were reported in a subgroup of trials with dual hormone system used, where four out of seven trials achieved significant decrease in glucose variability [39, 42, 43, 47] and the remaining three studies revealed no significant difference in glucose variability [30, 33, 48].

DISCUSSION

Closed-loop glucose control represents the state-of-the art in type 1 diabetes management and with rapid development in recent years promises to become a part of unsupervised clinical care [53, 54]. Current data almost unanimously support the use of closed-loop as safe and efficacious therapeutic option, with clinically relevant improvement in time spent in target range. Recent meta-analysis showed clinically significant improvement of more than 12 % of time spent in target range with the use of closed-loop systems compared to glucose control without computer algorithm [55], and without increased risk of hypoglycemia or blood glucose excursions. This was achieved with both dual-hormone and single-hormone system. Head to head comparison between both systems revealed slight difference favoring dual-hormone system [52]. Closed-loop glucose control was effective also in reducing time in hypoglycemia. The difference was more pronounced for the overnight period. There was little improvement in time in range or time in hypoglycemia compared to LGS systems. However, closed-loop reduced glucose variability, which can be harmful for developing brain in children.

As this glycemic outcome was not accessed in all trials, it is impossible to draw generalized conclusions on the main question of this review. Also within this review we didn't estimate the effectiveness of closed-loop systems in compare with conventional CSII by HbA1c because of the extremely short duration of published RCTs.

Due to lack in consistency in terms of reporting basic glycemic outcome measures between study reports, a consensus statement was published recently to enable unified outcomes reporting and with it easier interpretation of study results and widespread use to improve the lives of people with type 1 diabetes [22].

CONCLUSION

Much work has been done to develop effective and safe artificial pancreas, but not all RCTs confirmed advantages of closed-loop glucose control in compare with CSII in children and adolescents in real life. Absence of uniform methodology for glycemic control assessment (glycemic variability indexes, target ranges, hypo- and hyperglycaemia levels) makes impossible a quantitative comparison of different RCTs results. Further RCTs with a uniform methodology for glycemic control assessment required to prove benefits of closed-loop glucose control. Future researches should have also enough duration to make usable cumulative measures in a closed-loop efficacy estimation (HbA1c).

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